STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 163771

TO: Kevin Weddington **Location: rem/3A65/3C70** **Art Unit: 1614** **Tuesday, October 18, 2005** **Case Serial Number: 10/674145**	**From: Edward Hart** **Location: Biotech-Chem Library** **REM-1A55** **Phone: 571-272-2512** **edward.hart@uspto.gov**

Search Notes

Examiner Weddington,

Here are the results of the search you requested.

Please feel free to contact me if you have any questions.

Edward Hart

REM - 3C70

FOR OFFICIAL USE ONLY

ACCESS DB # 168771

PLEASE PRINT CLEARLY

Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: K. Weddington Examiner #: 68082 Date: 10-17-05

Art Unit: 1614 Phone Number: 2-0587 Serial Number: 10/674,145

Location (Bldg/Room#): 3A65 (Mailbox #): _____ Results Format Preferred (circle): PAPER DISK

****

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following: MEJ

Title of Invention: _____

Inventors (please provide full names): Doug A. Kaufmann

_____

Earliest Priority Date: _____

Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

A method of treating cancer with an antifungal agent.

****

STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: _____	____ NA Sequence (#)	(STN) ____ Dialog
Searcher Phone #: _____	____ AA Sequence (#)	____ Questel/Orbit ____ Lexis/Nexis
Searcher Location: _____	____ Structure (#)	____ Westlaw ____ WWW/Internet
Date Searcher Picked Up: 10/18/05	____ Bibliographic	____ In-house sequence systems
Date Completed: 10/18/05	____ Litigation	____ Commercial ____ Oligomer ____ Score/Length
Searcher Prep & Review Time: _____	____ Fulltext	____ Interference ____ SPDI ____ Encode/Transl
Online Time: _____	____ Other	____ Other (specify)

```
=> file medline
FILE 'MEDLINE' ENTERED AT 15:47:59 ON 18 OCT 2005

 FILE LAST UPDATED: 15 OCT 2005 (20051015/UP). FILE COVERS 1950 TO DATE.

 On December 19, 2004, the 2005 MeSH terms were loaded.

 The MEDLINE reload for 2005 is now available. For details enter HELP
 RLOAD at an arrow promt (=>). See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

 OLDMEDLINE now back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2005 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d his

     (FILE 'HOME' ENTERED AT 14:43:11 ON 18 OCT 2005)
               SET COST OFF

     FILE 'MEDLINE' ENTERED AT 14:43:23 ON 18 OCT 2005
               E KAUFMANN D/AU
L1           65 S E3-E4
               E ANTIFUNGAL/CT
L2       125184 S E4+NT/CT
L3        58867 S L2 /MAJ
L4      1604334 S C4./CT
L5      1341455 S L4 /MAJ
L6       195170 S (C4. (L) DT)/CT
L7         2489 S L3 AND L5
L8          682 S L6/MAJ AND L7
L9          176 S L8 NOT AB/FA
L10         506 S L8 NOT L9
L11         489 S ((ANTIFUNGAL AGENTS + NT) (L) (TU OR AD OR PD OR PK))/CT AND
L12       89191 S ((ANTIFUNGAL AGENTS + NT) (L) (TU OR AD OR PD OR PK))/CT
L13         454 S L12/MAJ AND L10
L14      195170 S (C4.(L) DT)/CT
L15         454 S L14/MAJ AND L13
L16         422 S L15/ENG
               E REVIEW/DT
L17          31 S E3-E8 AND L16
L18         357 S L16 AND PY<=2003
L19          20 S L17 AND L18
               E  CLINICAL TRIALS/CT
               E E3+ALL
L20          50 S E33+NT AND L18

     FILE 'MEDLINE' ENTERED AT 15:47:59 ON 18 OCT 2005

=> d ibib abs l19 tot

L19  ANSWER 1 OF 20     MEDLINE on STN
ACCESSION NUMBER:   2003332788     MEDLINE
```

DOCUMENT NUMBER: PubMed ID: 12864941
TITLE: Mammalian target of rapamycin: a new molecular target for breast cancer.
AUTHOR: Mita Monica M; Mita Alain; Rowinsky Eric K
CORPORATE SOURCE: Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, TX, USA.. mmita@idd.org
SOURCE: Clinical breast cancer, **(2003 Jun)** 4 (2) 126-37.
Ref: 148
Journal code: 100898731. ISSN: 1526-8209.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20030717
Last Updated on STN: 20031107
Entered Medline: 20031106

AB The mammalian target of rapamycin (mTOR), a downstream effector of the phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B) signaling pathway that mediates cell survival and proliferation, is a prime strategic target for anticancer therapeutic development. By targeting mTOR, the immunosuppressant and antiproliferative agent rapamycin inhibits signals required for cell cycle progression, cell growth, and proliferation. Both rapamycin and novel rapamycin analogues with more favorable pharmaceutical properties, such as CCI-779, RAD 001, and AP23573, are highly specific inhibitors of mTOR. In essence, these agents gain function by binding to the immunophilin FK506 binding protein 12 and the resultant complex inhibits the activity of mTOR. Because mTOR activates both the 40S ribosomal protein S6 kinase (p70s6k) and the eukaryotic initiation factor 4E-binding protein-1, rapamycin-like compounds block the actions of these downstream signaling elements, which results in cell cycle arrest in the G1 phase. Rapamycin and its analogues also prevent cyclin-dependent kinase (CDK) activation, inhibit retinoblastoma protein phosphorylation, and accelerate the turnover of cyclin D1, leading to a deficiency of active CDK4/cyclin D1 complexes, all of which potentially contribute to the prominent inhibitory effects of rapamycin at the G1/S boundary of the cell cycle. Rapamycin and rapamycin analogues have demonstrated impressive growth-inhibitory effects against a broad range of human cancers, including breast cancer, in preclinical and early clinical evaluations. In breast cancer cells, PI3K/Akt and mTOR pathways seem to be critical for the proliferative responses mediated by the epidermal growth factor receptor, the insulin growth factor receptor, and the estrogen receptor. Furthermore, these pathways may be constitutively activated in cancers with many types of aberrations, including those with loss of PTEN suppressor gene function. Therefore, the development of inhibitors of mTOR and related pathways is a rational therapeutic strategy for breast and other malignancies that possess a wide range of aberrant molecular constituents. This review will summarize the principal mechanisms of action of rapamycin and rapamycin derivatives, as well as the potential utility of these agents as anticancer therapeutic agents with an emphasis on breast cancer. The preliminary results of early clinical evaluations with rapamycin analogues and the unique developmental challenges that lie ahead will also be discussed.

L19 ANSWER 2 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2003154292 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12670453

TITLE: Pneumocystis carinii pneumonia prophylaxis in HIV negative patients with primary CNS lymphoma.
AUTHOR: Mathew Beela S; Grossman Stuart A
CORPORATE SOURCE: Regional Cancer Center, Trivandrum, India.
SOURCE: Cancer treatment reviews, **(2003 Apr)** 29 (2) 105-19. Ref: 179
Journal code: 7502030. ISSN: 0305-7372.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030403
Last Updated on STN: 20030531
Entered Medline: 20030530

AB Primary central nervous system lymphoma (PCNSL) is an uncommon malignant brain tumor, which is increasing in incidence in immunocompetent individuals. In the recent past, the survival at 5 years was less than 5% when this cancer was treated with radiation therapy and standard chemotherapy. Current high dose methotrexate-based regimens have resulted in median survival of 3-4 years and the 5-year survival approaches 40%. However, these potentially curable patients appear to be at significant risk for developing Pneumocystis carinii pneumonia (PCP), which has a mortality of nearly 50%. The major risk factors in this patient population appear to be glucocorticoids, high dose methotrexate, and radiation therapy all of which reduce CD4+ counts. Prophylaxis must be considered carefully because of the significant risk of drug interactions between the methotrexate and the antibiotics used to prevent Pneumocystis infections. This manuscript reviews the changing therapy for primary CNS lymphomas, the pathogenesis, diagnosis and treatment of P. carinii pneumonia, the potential interactions between methotrexate and prophylactic antibiotics, and the risk of Pneumocystis infection in these patients. It also provides recommendations for Pneumocystis prophylaxis for this patient population.

L19 ANSWER 3 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2002451882 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12211424
TITLE: CCI-779 Wyeth.
AUTHOR: Elit Laurie
CORPORATE SOURCE: Hamilton Regional Cancer Center, Ontario, Canada.. laurie.elit@hrcc.on.ca
SOURCE: Current opinion in investigational drugs (London, England : 2000), **(2002 Aug)** 3 (8) 1249-53. Ref: 38
Journal code: 100965718. ISSN: 1472-4472.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20020906
Last Updated on STN: 20030319
Entered Medline: 20030318

AB Wyeth Research (formerly Wyeth-Ayerst Research) is developing the sirolimus (rapamycin) analog CCI-779 as a potential treatment for various cancers [320924]. By November 2001, phase III trials had been initiated

[428972], [429576]. In October 2001, Raymond James predicted filing in 2003, with a potential launch in 2005 [426718]. In March 2002, CCI-779, was designated for fast-track development by the FDA for the treatment of renal cell carcinoma after failure of initial therapy [442535]; at this time phase III trials for renal cell carcinoma and phase II trials for various solid tumors were ongoing [444030]. In March 2002, Wyeth revealed that filing was anticipated for 2004/2005 [443491]. In June and August 2001, Lehman Brothers predicted sales of US $40 million ($20 million in the US) in 2003, rising to US $75 million ($38 million in the US) in 2004 [418901], [420809]. In October 2001, analysts at Raymond James expected potential sales of the product at US $250 million [426718]. In May 2002, a patent (WO-00240000) was published claiming CCI-779 to be useful for the treatment of cancers of various origins, including renal, breast, cervical, uterine, head and neck, lung, prostate, pancreatic, ovarian, colon, lymphoma and melanoma.

L19 ANSWER 4 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2002389325 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12137719
TITLE: Interventions for preventing oral candidiasis for patients with cancer receiving treatment.
COMMENT: Comment in: ACP J Club. 2003 Mar-Apr;138(2):46. PubMed ID: 12614131
Update in: Cochrane Database Syst Rev. 2004;(4):CD003807. PubMed ID: 15495065
AUTHOR: Worthington H V; Clarkson J E; Eden O B
CORPORATE SOURCE: Oral Health and Development, University Dental Hospital of Manchester, Higher Cambridge Street, Manchester, UK, M15 6FH.. helen.worthington@man.ac.uk
SOURCE: Cochrane database of systematic reviews (Online : Update Software), **(2002)** (3) CD003807. Ref: 64
Journal code: 100909747. ISSN: 1469-493X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(META-ANALYSIS)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020725
Last Updated on STN: 20030326
Entered Medline: 20020924

AB BACKGROUND: Treatment of cancer is increasingly more effective but is associated with short and long-term side effects. Oral side effects remain a major source of illness despite the use of a variety of agents to prevent and treat them. One of these side effects is oral candidiasis. OBJECTIVES: To assess the effectiveness of interventions (which may include placebo or no treatment) for the prevention of oral candidiasis for patients with cancer receiving chemotherapy and or radiotherapy. SEARCH STRATEGY: Electronic databases : Cochrane Oral Health Group Specialised Register, CCTR, MEDLINE and EMBASE were searched. Date of the most recent searches May 2001 (CCTR 2001, issue 3). SELECTION CRITERIA: Trials were selected if they met the following criteria: design - random allocation of participants; participants - anyone receiving chemotherapy or radiotherapy treatment for cancer; interventions - agents prescribed to prevent oral candidiasis; primary outcome - prevention of oral candidiasis. DATA COLLECTION AND ANALYSIS: Data were recorded on the following secondary outcomes if present: relief of pain, amount of analgesia, relief of dysphagia, incidence of systemic infection, duration

of stay in hospital (days), cost of oral care, patient quality of life, death, use of empirical antifungal treatment, toxicity and compliance. Information regarding methods, participants, interventions, outcome measures and results were independently extracted, in duplicate, by two reviewers (HW & JC). The Cochrane Oral Health Group statistical guidelines were followed and relative risk values calculated using random effects models where significant heterogeneity was detected (P<0.1). Potential sources of heterogeneity were examined in random effects meta-regression analyses. MAIN RESULTS: Twenty-seven trials involving 4,137 patients satisfied the inclusion criteria. Drugs absorbed and partially absorbed from the GI tract were found to prevent oral candidiasis when compared to a placebo, or a no treatment control group, with RR for absorbed drugs =0.45 (95%CI 0.31 to 0.64). For absorbed drugs in populations with an incidence of 20% (mid range of results in control groups), this implies a NNT of 9 (95%CI 7 to 13) patients need to be treated to avoid one patient getting oral candidiasis. There was no significant benefit for drugs not absorbed from the GI tract. REVIEWER'S CONCLUSIONS: There is strong evidence, from randomised controlled trials, that drugs absorbed or partially absorbed from the GI tract prevent oral candidiasis in patient receiving treatment for cancer. There is also evidence that these drugs are significantly better at preventing oral candidiasis than drugs not absorbed from the GI.

L19 ANSWER 5 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2002278065 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12020063
TITLE: Inhibitors of mammalian target of rapamycin as novel antitumor agents: from bench to clinic.
AUTHOR: Huang Shile; Houghton Peter J
CORPORATE SOURCE: Department of Molecular Pharmacology, St Jude Children's Research Hospital, Memphis, TN 38105-2794, USA.
CONTRACT NUMBER: CA23099 (NCI)
CA28765 (NCI)
CA77776 (NCI)
SOURCE: Current opinion in investigational drugs (London, England : 2000), **(2002 Feb)** 3 (2) 295-304. Ref: 90
Journal code: 100965718. ISSN: 1472-4472.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20020522
Last Updated on STN: 20021218
Entered Medline: 20021217

AB Rapamycin and its derivatives, CCI-779 and RAD-001, inhibit the mammalian target of rapamycin (mTOR), downregulating translation of specific mRNAs required for cell cycle progression from G1 to S phase. Preclinically, mTOR inhibitors potently suppress growth and proliferation of numerous tumor cell lines in culture or when grown in mice as xenografts. CCI-779 and RAD-001 are being developed as antitumor drugs and are undergoing clinical trials. Clinically, CCI-779 has shown evidence of antitumor activity but induced relatively mild side effects in patients. Here we discuss potential antitumor mechanisms and resistance mechanisms of mTOR inhibitors, and summarize the current status of these compounds as novel antitumor agents.

L19 ANSWER 6 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2002100739 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11831650
TITLE: Resistance to rapamycin: a novel anticancer drug.
AUTHOR: Huang S; Houghton P J
CORPORATE SOURCE: Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN 38105-2794, USA.
CONTRACT NUMBER: CA23099 (NCI)
CA28765 (NCI)
CA77776 (NCI)
SOURCE: Cancer and metastasis reviews, **(2001)** 20 (1-2) 69-78. Ref: 92
Journal code: 8605731. ISSN: 0167-7659.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020208
Last Updated on STN: 20020731
Entered Medline: 20020730
AB The macrocyclic lactone rapamycin has an established place as an immune suppressive agent in organ transplantation. However, more recently it has been recognized as an inhibitor of pathways that may be activated during malignant transformation and tumor progression. Thus, increasing interest is being directed to this class of antibiotic as potential antitumor agents. Here we summarize the history, mechanism of action, and mechanisms of resistance to rapamycin.

L19 ANSWER 7 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2001457323 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11502466
TITLE: Rationale for combination ketoconazole/ vitamin D treatment of prostate cancer.
AUTHOR: Peehl D M; Seto E; Feldman D
CORPORATE SOURCE: Department of Urology, Stanford University School of Medicine, Stanford, California, USA..
dpeehl@leland.stanford.edu
SOURCE: Urology, **(2001 Aug)** 58 (2 Suppl 1) 123-6. Ref: 24
Journal code: 0366151. ISSN: 1527-9995.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010815
Last Updated on STN: 20011029
Entered Medline: 20011025
AB The high rate of progression of prostate cancer after androgen deprivation therapy mandates that new strategies be developed. Adjuvant therapy combined with androgen deprivation may slow or prevent progression. Ketoconazole plus calcitriol therapy is an example of 1 such a combination with a mechanistic basis for synergistic activity. Ketoconazole is commonly used as a second-line androgen deprivation therapy. This

imidazole derivative is an inhibitor of P-450 enzymes, including those involved in steroidogenesis. Other P-450 enzymes that are inhibited by ketoconazole include 1alpha-hydroxylase and 24-hydroxylase, which metabolize vitamin D. Growth inhibition of prostate cancer cells by vitamin D depends on levels of the active metabolite, 1,25-dihydroxyvitamin D(3) (calcitriol). The enzyme 24-hydroxylase converts calcitriol to less active products. The inhibition of 24-hydroxylase by ketoconazole maintains the magnitude and duration of response to calcitriol. Combined ketoconazole/calcitriol therapy might therefore potentiate the antitumor activity of calcitriol. Because androgen-independent prostate cancer cells often remain responsive to growth inhibition by calcitriol, it is also possible that calcitriol would slow or prevent development of androgen-independent cancer growth. Another consideration is that ketoconazole blocks 1alpha-hydroxylase activity, which is the key enzyme that creates calcitriol in the body. Therefore, patients receiving ketoconazole therapy are likely to be deficient in vitamin D. The detrimental consequences of vitamin D deficiency in these patients would also be alleviated by the addition of calcitriol to the therapeutic regimen.

L19 ANSWER 8 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2001435625 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11333134
TITLE: Oral antifungals as prophylaxis in haematological malignancy.
AUTHOR: Prentice A G; Donnelly P
CORPORATE SOURCE: Clinical Haematology Unit, Derriford Hospital, Plymouth, UK.. archie.prentice@phnt.swest.nhs
SOURCE: Blood reviews, **(2001 Mar)** 15 (1) 1-8. Ref: 73
Journal code: 8708558. ISSN: 0268-960X.
PUB. COUNTRY: Scotland: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802

AB In the standard treatment of patients with haematological malignancy, immunosuppressive therapy produces prolonged periods of neutropenia and mucositis, which increase the risk of systemic fungal infection. In allogeneic bone marrow transplantation, this risk extends well beyond the period of neutropenia when graft-versus-host disease, and its treatment, result in prolonged lymphocytopenia. Various agents are used for antifungal prophylaxis and treatment but all have limitations: amphotericin B is restricted by the need for intravenous infusion and the occurrence of adverse events, fluconazole by its narrow spectrum of activity and the emergence of fluconazole-resistant fungi and itraconazole capsules by erratic absorption. Oral administration of antifungals has clear advantages in prophylaxis and an important current strategy is to maximize the extent and reliability of the oral bioavailability of antifungal agents. Mucositis is the main obstacle for success of strategies based on oral delivery. In this review, the ability of these new oral formulations to deliver sufficient antifungal prophylaxis is evaluated.

L19 ANSWER 9 OF 20 MEDLINE on STN
ACCESSION NUMBER: 1999119008 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9922035
TITLE: Relapsed acute promyelocytic leukemia previously treated with all-trans retinoic acid: clinical experience with a new synthetic retinoid, Am-80.
AUTHOR: Takeuchi M; Yano T; Omoto E; Takahashi K; Kibata M; Shudo K; Harada M; Ueda R; Ohno R
CORPORATE SOURCE: Department of Internal Medicine, National Sanatorium Minami Okayama Hospital, Tsukubo Gun, Japan.
SOURCE: Leukemia & lymphoma, **(1998 Nov)** 31 (5-6) 441-51.
Ref: 53
Journal code: 9007422. ISSN: 1042-8194.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: (CASE REPORTS)
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990525
Last Updated on STN: 19990525
Entered Medline: 19990513

AB All-trans retinoic acid (ATRA), a potent differentiating drug for acute promyelocytic leukemia (APL), induces a high incidence of complete remission (CR) in patients with APL and is now established as a first-line therapy. However, ATRA resistance has become a clinical problem. Patients who relapsed after ATRA-induced CR have had difficulty in obtaining a second CR with ATRA therapy. Although several mechanisms have been postulated, treatment strategies to overcome resistance have not been established. We used a new synthetic retinoid, Am-80, as reinduction therapy for APL relapse after from ATRA-induced CR. Am-80 was several times more potent than ATRA in inducing differentiation in vitro. At a 6 mg/m2 dose, there were 24 evaluable patients; 14 (58%) achieved CR between days 20 and 58 (median, 37 days). Clinical response correlated with the in vitro response to Am-80. Adverse effects included retinoic acid syndrome (n = 1), hyperleukocytosis (n = 1), xerosis (n = 9), cheilitis (n = 8), hypertriglyceridemia (n = 16), and hypercholesterolemia (n = 15). Am-80 is active in APL after relapse from ATRA-induced CR. Further clinical trials are needed to establish strategies to overcome ATRA resistance.

L19 ANSWER 10 OF 20 MEDLINE on STN
ACCESSION NUMBER: 1998080191 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9420024
TITLE: Trimetrexate: experience with solid tumors.
AUTHOR: Haller D G
CORPORATE SOURCE: Department of Medicine, University of Pennsylvania Cancer Center, The University of Pennsylvania School of Medicine, Philadelphia 19104, USA.
SOURCE: Seminars in oncology, **(1997 Oct)** 24 (5 Suppl 18) S18-71-S18-76. Ref: 28
Journal code: 0420432. ISSN: 0093-7754.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980114

AB Trimetrexate (TMTX), a potent inhibitor of the enzyme dihydrofolate reductase, is biochemically and metabolically similar to methotrexate (MTX). Fundamental differences between TMTX and MTX, however, mandate investigation of TMTX in both MTX-sensitive and MTX-resistant tumors. In a number of phase II clinical trials, the antitumor activity of single-agent TMTX has been variable, in part because of the heterogeneity of doses and schedules used and in part because of diverse patient populations. Single-agent activity has been documented in some commonly occurring tumors, including breast, non-small cell lung, and head and neck cancers. Other tumors with sensitivity to single-agent TMTX include transitional cell carcinomas of the urothelium, prostate cancer, and gastric carcinoma. In a small series of children with renal cell carcinoma, significant clinical activity was suggested. The single-agent activity of TMTX, coupled with the finding that TMTX may act as a biochemical modulator of 5-fluorouracil/leucovorin, suggests that the addition of TMTX to 5-fluorouracil/leucovorin should be investigated further. The possibility that TMTX may both exhibit single-agent activity and modulate the effectiveness of other agents makes combination therapy attractive.

L19 ANSWER 11 OF 20 MEDLINE on STN
ACCESSION NUMBER: 1998080189 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9420022
TITLE: Trimetrexate: review and current clinical experience in advanced colorectal cancer.
AUTHOR: Blanke C D; Messenger M; Taplin S C
CORPORATE SOURCE: Department of Medicine, The Vanderbilt Cancer Center, Nashville, TN, USA.
SOURCE: Seminars in oncology, **(1997 Oct)** 24 (5 Suppl 18) S18-57-S18-63. Ref: 42
Journal code: 0420432. ISSN: 0093-7754.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980114

AB Unresectable metastatic colorectal cancer remains a significant cause of morbidity and mortality in both the United States and Europe. To date, no chemotherapeutic regimen for this disease has demonstrated a definitive survival advantage compared with 5-fluorouracil (5-FU) plus leucovorin (LV). However, recent trials have raised the possibility that the combination of trimetrexate (TMTX) plus 5-FU/LV may improve response rates and survival in patients with metastatic colorectal cancer. Trimetrexate is a nonclassical antifolate that has demonstrated antitumor activity against a number of malignancies, including those resistant to the classical antifolate methotrexate. While the single-agent activity of TMTX remains modest in metastatic colorectal cancer, the combination of TMTX/5-FU/LV has shown significant activity in several phase II trials.

Reported studies include a phase II trial in chemotherapy failures that demonstrated a 20% response rate, and two multicenter phase II trials in previously untreated patients that demonstrated 50% and 38% overall response rates, respectively. Diarrhea was the dose-limiting toxicity in all trials, although a regimen of scheduled loperamide was quite effective in mitigating this complication. These studies are being followed up with two confirmatory phase II studies in chemorefractory patients and two randomized phase III trials comparing TMTX/5-FU/LV with standard 5-FU/LV.

L19 ANSWER 12 OF 20 MEDLINE on STN
ACCESSION NUMBER: 1998080188 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9420021
TITLE: Biomodulation of 5-fluorouracil with antifolates.
AUTHOR: Bertino J R
CORPORATE SOURCE: Program of Molecular Pharmacology and Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.
CONTRACT NUMBER: CA 61586 (NCI)
SOURCE: Seminars in oncology, **(1997 Oct)** 24 (5 Suppl 18) S18-52-S18-56. Ref: 29
Journal code: 0420432. ISSN: 0093-7754.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980114

AB The cytotoxic activity of 5-fluorouracil (5-FU) can be modulated by coadministration of antifolates or leucovorin (LV). Although a recent meta-analysis concluded that a sequential combination of methotrexate (MTX) and 5-FU was superior to 5-FU alone in terms of response rate and survival, combination MTX and 5-FU therapy has not been actively pursued by many leading cancer centers. We have subsequently investigated the combination of trimetrexate (TMTX) plus 5-FU/LV. Unlike MTX, TMTX does not compete with LV for uptake or polyglutamylation. In a phase I clinical study, combination TMTX/5-FU/LV was well tolerated and produced an overall response rate of 20% in previously treated colorectal cancer patients. In a follow-up phase II clinical study, this combination was highly active in patients with advanced colorectal cancer, demonstrating a 50% overall response rate. Currently, a phase III clinical trial is in progress comparing this regimen with combination 5-FU/LV.

L19 ANSWER 13 OF 20 MEDLINE on STN
ACCESSION NUMBER: 96422504 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8825121
TITLE: Immunomodulation following chemotherapy.
AUTHOR: Obadina M; Verma U; Hawkins M; Mazumder A
CORPORATE SOURCE: Vincent T. Lombardi Cancer Research Center, Georgetown University Hospital, Washington, DC, USA.
SOURCE: Breast cancer research and treatment, **(1996)** 38 (1) 41-8. Ref: 44
Journal code: 8111104. ISSN: 0167-6806.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961114

AB In the last decade, immunomodulation has emerged as a mode of therapy capable of mediating the regression of cancer in some patients. This article reviews our experience with immunomodulation following transplant and non-transplant chemotherapy. We used interferon and cyclosporine A following conventional chemotherapy in a non-transplant setting for a B16 melanoma in a murine model. This combination generated cells with MHC-unrestricted cytotoxicity. We have also used immunotherapy in the transplant setting with IL-2 activated PBSC in patients with breast cancer. Of the 28 patients treated, 20 developed GVHD and the average time to reconstitution was 12 days (comparable to a control group). This article also raises the possibility of extending immunomodulation to breast cancer patients in the nontransplant setting to induce an antitumor immune response following cytoreductive chemotherapy.

L19 ANSWER 14 OF 20 MEDLINE on STN
ACCESSION NUMBER: 96223347 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8630924
TITLE: Cisplatin-based chemotherapy in renal transplant recipients. A case report and a review of the literature.
AUTHOR: Benisovich V I; Silverman L; Slifkin R; Stone N; Cohen E
CORPORATE SOURCE: Department of Medicine, Mount Sinai Medical Center, New York, New York, USA.
SOURCE: Cancer, **(1996 Jan 1)** 77 (1) 160-3. Ref: 22
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW OF REPORTED CASES)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960715
Last Updated on STN: 19960715
Entered Medline: 19960701

AB BACKGROUND. Renal transplant recipients have a high incidence of cancer. The main side effect of cisplatin, nephrotoxicity, has special implications in renal transplant recipients. This is particularly true in view of the routine use of cyclosporine as an immunosuppresant. Nephrotoxicity is also one of the main side effects of cyclosporine. METHODS. We report a patient with a renal allograft who was receiving cyclosporine for immunosuppression and developed metastatic transitional cell carcinoma of the bladder and was treated with cisplatin-based chemotherapy. The literature regarding cisplatin-containing chemotherapy in patients with different cancers and a single transplanted kidney is reviewed. RESULTS. The patient received four cycles of methotrexate, vinblastine, doxorubicin, and cisplatin while on continuous cyclosporine therapy. His renal function remained stable. He responded to chemotherapy initially, but this response was short. Ten patients with renal transplants and cancer who were treated with cisplatin have been reported previously. Two were maintained on cyclosporine for immunosuppression throughout chemotherapy. No patient developed renal

failure during or shortly after administration of cisplatin. Two of five patients treated for testicular cancer developed renal failure at 3 and 6 years after completion of chemotherapy. However, in both cases the cause of renal failure was attributed to chronic rejection of the transplanted kidney. CONCLUSION. Renal transplant recipients usually tolerate cisplatin-based chemotherapy well. It should be offered to patients with potentially curable cancer (e.g., germ cell tumor). This case and a review of the literature suggest that these patients retain baseline renal function even if cisplatin-based chemotherapy and cyclosporine are given simultaneously.

L19 ANSWER 15 OF 20 MEDLINE on STN
ACCESSION NUMBER: 95087500 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7995181
TITLE: Endoscopic and histologic resolution of gastric pseudolymphoma (reactive lymphoid hyperplasia) following treatment with bismuth and oral antibiotics.
AUTHOR: Weston A P; Campbell D R; McGregor D H; Cherian R
CORPORATE SOURCE: Division of Gastroenterology, University of Kansas School of Medicine, Kansas City.
SOURCE: Digestive diseases and sciences, **(1994 Dec)** 39 (12) 2567-74. Ref: 44
Journal code: 7902782. ISSN: 0163-2116.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW OF REPORTED CASES)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950126
Last Updated on STN: 19970203
Entered Medline: 19950117

AB Gastric pseudolymphoma is a rare disorder of unknown etiology that can undergo transformation into malignant lymphoma. This report describes the first case of a gastric pseudolymphoma associated with Helicobacter pylori infection that underwent complete clinical, endoscopic, and histologic resolution following treatment with bismuth subsalicylate, amoxicillin, and metronidazole. The eradication of Helicobacter pylori may have eliminated ongoing antigenic stimulation that has previously been postulated to be responsible for the development and subsequent progression of gastric pseudolymphoma.

L19 ANSWER 16 OF 20 MEDLINE on STN
ACCESSION NUMBER: 94252015 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8194282
TITLE: Clinical pharmacokinetics and pharmacology of trimetrexate.
AUTHOR: Marshall J L; DeLap R J
CORPORATE SOURCE: Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, DC.
SOURCE: Clinical pharmacokinetics, **(1994 Mar)** 26 (3) 190-200. Ref: 61
Journal code: 7606849. ISSN: 0312-5963.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940707
Last Updated on STN: 19940707
Entered Medline: 19940624

AB Trimetrexate represents one of a number of new antimetabolites that have been studied in malignant, rheumatological and infectious disease. Methotrexate, the classical antifolate agent, is active in a broad spectrum of clinical settings, but its use is limited ny pre-existing or acquired cellular resistance. Trimetrexate is an agent that does not require uptake by the folate carrier transport system, a major mechanism of cellular resistance both in vitro and in vivo. Both dihydrofolate reductase inhibition and high performance liquid chromatography (HPLC) assays can be used to determine drug concentrations. Clearance of trimetrexate has been reported to follow biphasic or triphasic patterns. Elimination is primarily by biotransformation with less than 5% of the drug excreted renally in an unchanged form. Both active and inactive metabolites have been found, but the precise metabolic pathways have yet to be defined. The role of trimetrexate in the treatment of Pneumocystis carinii pneumonia is limited to compassionate use, as clinical studies have shown cotrimoxazole (trimethoprim-sulfamethoxazole) to be superior to trimetrexate. However, in a wide spectrum of malignant processes, trimetrexate appears to have a role either as a high-dose single agent, with calcium folinate (leucovorin calcium) rescue, or in combination with other antineoplastic agents. However, further trials are needed to fully establish the efficacy of trimetrexate in these settings. Increased knowledge of the pattern of resistance for individual tumours and tumour types may result in trimetrexate becoming more widely used clinically.

L19 ANSWER 17 OF 20 MEDLINE on STN
ACCESSION NUMBER: 93153725 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8428329
TITLE: Ketoconazole and liarozole in the treatment of advanced prostatic cancer.
AUTHOR: Mahler C; Verhelst J; Denis L
CORPORATE SOURCE: Department of Endocrinology, A. Z. Middelheim, Antwerp, Belgium.
SOURCE: Cancer, **(1993 Feb 1)** 71 (3 Suppl) 1068-73. Ref: 49
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199303
ENTRY DATE: Entered STN: 19930326
Last Updated on STN: 19960129
Entered Medline: 19930308

AB BACKGROUND. Ketoconazole, an imidazole derivative, is an orally active antifungal agent. In high doses (400 mg three times a day), it inhibits the biosynthesis of testicular and adrenal androgens and may therefore be useful for the treatment of hormone dependent diseases such as advanced prostatic cancer. Similarly, a new imidazole derivative, liarozole, was recently found to interfere with testicular and adrenal steroid biosynthesis in animals and healthy volunteers. METHODS. The therapeutic and endocrine effects of ketoconazole and liarozole in patients with

disseminated prostatic cancer are discussed, including data from the literature and personal experience. RESULTS. Using high-dose ketoconazole, medical castration with the expected clinical response was achieved easily in previously untreated patients in all clinical series (personal data include seven patients). In patients with prostatic cancer who had relapses after castration, few objective remissions were achieved. By contrast, long-lasting subjective remissions, especially pain relief, were seen in more than half of the patients (personal data include 20 patients). Gastrointestinal intolerance, which was the main side effect, severely limits the routine use of the drug. Recently, the authors studied the effect of liarozole on adrenal steroid production in castrated patients whose disease was progressive after first-line treatment. Unlike ketoconazole therapy, adrenal androgen and cortisol levels were not modified. A Phase I-II trial was then done in 44 patients with metastatic prostatic cancer in clinical relapse. In patients with measurable disease, objective responses, including tumoral volume reduction, occurred in approximatively 30%. A prostate specific antigen reduction of 50% or more was noted in approximatively 50% of patients. Pain relief occurred in most patients. Mucocutaneous side effects were observed in most patients--dryness of the skin and onychomalacia. Raised tissue retinoic acid levels suggested a possible pathway by which this drug might exert its cytotoxic effects. CONCLUSIONS. Ketoconazole in high doses is effective in first-line and second-line therapy for advanced prostatic cancer, but gastrointestinal side effects limit its routine use. Liarozole is a new imidazole that is also effective in second-line therapy for prostatic cancer and has fewer side effects. Unlike ketoconazole, its effect is not mediated by inhibition of steroid biosynthesis.

L19 ANSWER 18 OF 20 MEDLINE on STN
ACCESSION NUMBER: 92287766 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1534671
TITLE: Approaches to management of fungal infections in cancer patients.
AUTHOR: Francis P; Walsh T J
CORPORATE SOURCE: Infectious Diseases Section, National Cancer Institute, Bethesda, Maryland.
SOURCE: Oncology (Williston Park, N.Y.), **(1992 May)** 6 (5) 133-44; discussion 144, 147-8. Ref: 117
Journal code: 8712059. ISSN: 0890-9091.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920724
Last Updated on STN: 19920724
Entered Medline: 19920714

AB The patient most susceptible to invasive aspergillosis has had prolonged granulocytopenia resulting from intensive chemotherapy and/or radiation therapy, aplastic anemia, or acute leukemia. The sinuses and lungs are usually involved, but the infection may disseminate to the endocardium, skin, CNS, and eye. Efficacy of antifungal treatment with amphotericin B depends on early recognition and aggressive intervention. In severe or refractory cases, addition of flucytosine, rifampin, or fluconazole may be beneficial. The most ominous presentation of zygomycosis involves sinus and orbital destruction and necrosis. However, pulmonary involvement is the most common manifestation in cancer patients. Infections with

Pseudallescheria boydii, Fusarium species, and Trichosporon beigelii are increasingly being recognized in cancer patients, as are Malassezia furfur and invasive mycoses from dematiaceous molds.

L19 ANSWER 19 OF 20 MEDLINE on STN
ACCESSION NUMBER: 89280076 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2659829
TITLE: High dose ketoconazole for the treatment of hormone refractory metastatic prostate carcinoma: 16 cases and review of the literature.
AUTHOR: Jubelirer S J; Hogan T
CORPORATE SOURCE: Cancer Care Center of Southern West Virginia, Charleston Area Medical Center.
SOURCE: Journal of urology, **(1989 Jul)** 142 (1) 89-91.
Ref: 91
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW OF REPORTED CASES)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198907
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19900309
Entered Medline: 19890725

AB We treated 16 patients who had hormone refractory metastatic prostate cancer with 400 mg. ketoconazole orally every 8 hours. None of the patients had an objective response, although 6 (37.5 per cent) had stable disease (2 of whom had a subjective decrease in bone pain). The median duration of stable disease was 6.8 months (range 2 to 12 months) and side effects were seen in 14 patients. Nausea, vomiting or anorexia was noted in 10 patients, rash and pruritus in 2, transient abnormal liver function tests in 1 and transient pulmonary infiltrates in 1. Nine prior studies investigating the use of ketoconazole in hormone refractory metastatic prostate cancer were reviewed. Only 1 complete response was reported. A partial response was noted in 14 per cent of the patients. Most of the patients had stable or progressive disease. High dose ketoconazole as a single agent appears to have limited use in patients who have failed prior systemic therapy.

L19 ANSWER 20 OF 20 MEDLINE on STN
ACCESSION NUMBER: 79234548 MEDLINE
DOCUMENT NUMBER: PubMed ID: 380801
TITLE: Azaserine, DON, and azotomycin: three diazo analogs of L-glutamine with clinical antitumor activity.
AUTHOR: Catane R; Von Hoff D D; Glaubiger D L; Muggia F M
SOURCE: Cancer treatment reports, **(1979 Jun)** 63 (6) 1033-8. Ref: 35
Journal code: 7607107. ISSN: 0361-5960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197910
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19970203
Entered Medline: 19791017

AB A review of the clinical data on azaserine, DON, and azotomycin reveals that these agents have limited but definite antitumor activity. All three drugs are analogs of L-glutamine and contain a diazo group. They have been studied as single agents in a wide variety of human malignancies and have also been included in trials using combination chemotherapy. Most of these studies were performed early in the history of clinical trials and, therefore, the method of reporting results and the evaluation criteria were quite different from those in use today. A renewed interest in these agents has been triggered by the remarkable activity of DON and azotomycin against human tumor lines implanted into nude mice. On the basis of this activity and the clinical data we have compiled, we feel that new clinical trials with these agents are warranted.

=> d ibib abs l20 tot

L20 ANSWER 1 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2003585784 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14666682
TITLE: Selectivity of action of glycyrrhizin derivatives on the growth of MCF-7 and HEP-2 cells.
AUTHOR: Rossi Tiziana; Castelli Mario; Zandomeneghi Ginevra; Ruberto Antonio; Benassi Luisa; Magnoni Cristina; Santachiara Saverio; Baggio Giosue
CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of Modena and Reggio Emilia, Modena, Italy.. rossi.tiziana@unimore.it
SOURCE: Anticancer research, **(2003 Sep-Oct)** 23 (5A) 3813-8.
Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 20031216
Last Updated on STN: 20040212
Entered Medline: 20040211

AB Since 1986, there have been reports in the literature that glycyrrhizin (GL), 18 alpha-glycyrrhetinic acid (18 alpha-GA) and 18 beta-glycyrrhetinic acid (18 beta-GA) can inhibit the growth of some murine tumours. Recently, testing the activity of GL and 18 alpha-GA on human tumour cells, we observed that both substances are good anti-proliferative agents, especially on those cells whose replication rate is slow. In the present study, the MTT test was performed on MCF-7, Hep-2 and VERO cells treated with increasing concentrations of GL and of its derivatives. Results showed that the substances do not have a toxic effect on VERO cells and that their anti-proliferative effect is evident only on the cell line (MCF-7) that evolves slowly. Finally, the TUNEL test revealed the presence of apoptosis in MCF-7 cells treated with dosages of GL and 18 alpha-GA, thereby confirming that these natural phytoestrogens could be considered as interesting new agents for cancer therapy.

L20 ANSWER 2 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2003496080 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14572867
TITLE: A novel sunscreen agent having antimelanoma activity.
AUTHOR: Nogueira Marisa A; Magalhaes Eva G; Magalhaes Aderbal F; Biloti Debora N; Laverde Antonio; Pessine Francisco B T;

Carvalho Joao E; Kohn Luciana K; Antonio Marcia A; Marsaioli Anita J
CORPORATE SOURCE: Instituto de Quimica, Universidade Estadual de Campinas, CP 6154, SP, 13083-970 Campinas, Brazil.
SOURCE: Farmaco (Societa chimica italiana : 1989), **(2003 Nov)** 58 (11) 1163-9.
Journal code: 8912641. ISSN: 0014-827X.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200407
ENTRY DATE: Entered STN: 20031024
Last Updated on STN: 20040707
Entered Medline: 20040706

AB A novel series of eight dibenzoylmethane derivatives having both sunscreen and cytotoxic activity has been obtained by derivatizing commercial dibenzoyl methanes. Four human cancer cell lines (MCF 7 (breast), NCI ADR (breast expressing the multidrug resistance phenotype), NCI 460 (lung) and UACC 62 (melanoma)) were used for the cytotoxic assay. Eight among the 19 dibenzoylmethane derivatives showed cytotoxicity against these four cell lines. Absorption spectroscopies revealed that these compounds can be used as sunscreens against UV radiation.

L20 ANSWER 3 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2003377240 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12912932
TITLE: Pharmacodynamic Evaluation of CCI-779, an Inhibitor of mTOR, in Cancer Patients.
COMMENT: Comment in: Clin Cancer Res. 2003 Aug 1;9(8):2882-6. PubMed ID: 12912931
AUTHOR: Peralba Josep Maria; DeGraffenried Linda; Friedrichs William; Fulcher Letitia; Grunwald Viktor; Weiss Geoffrey; Hidalgo Manuel
CORPORATE SOURCE: The University of Texas Health Science Center at San Antonio, Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, Texas, USA.
SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, **(2003 Aug 1)** 9 (8) 2887-92.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20030813
Last Updated on STN: 20040611
Entered Medline: 20040610

AB CCI-779 is an ester of rapamycin and inhibitor of mammalian target of rapamycin (mTOR) currently in Phase II clinical development for the treatment of patients with cancer. CCI-779 interacts with mTOR and inhibits its kinase activity, resulting in inhibition of the mTOR-regulated translational controllers p70(s6) kinase and 4E-BP1. Ultimately, CCI-779 decreases the translation of mRNAs involved in the control of the cell cycle, resulting in cell cycle arrest. The objective of this study was to develop a method to determine the pharmacodynamic effects of CCI-779 suitable for use in clinical trials. Exposure of Raji lymphoblastoid cells to increasing concentrations of rapamycin resulted in

a linear concentration-dependent inhibition of p70(s6) kinase activity, suggesting that p70(s6) kinase activity could be an appropriate marker for mTOR-interacting agents. In subsequent experiments, treatment of nude mice bearing the CCI-779 susceptible breast cancer cell line MDA-468 with a single dose of 10 mg/kg CCI-779 resulted in a >80% inhibition of p70(s6) kinase activity in peripheral blood mononuclear cells (PBMCs) 72 h after treatment. Importantly, the degree of p70(s6) kinase inhibition was identical in PBMCs and simultaneously collected tumor tissue, suggesting that the PBMCs are an adequate surrogate tissue for p70(s6) kinase activity in vivo. The intrasubject coefficient of variation of p70(s6) kinase activity measured in PBMCs collected from five healthy volunteers on days 1, 4, and 8 was 14%, indicating that p70(s6) kinase activity in PBMCs remains relatively stable over time. Finally, p70(s6) kinase activity was measured in PBMCs from nine patients with renal cell cancer treated with a single dose of 25, 75, or 250 mg of CCI-779 i.v. (three patients each). PBMCs were collected on days 2, 4, and 8 after CCI-779 treatment. In this small data set, eight of the nine patients had evidence of p70(s6) kinase activity inhibition after treatment that was independent of the administered dose. There was a significant linear association between time to disease progression and inhibition of p70(s6) kinase activity 24 h after treatment. In conclusion, these results indicate that the pharmacodynamic effects of CCI-779 can be determined using a p70(s6) kinase assay in PBMCs. This assay is currently being incorporated in Phase I and II studies with CCI-779 to determine its relationship with dose and plasma concentration of the agent and its value as a predictor of treatment efficacy.

L20 ANSWER 4 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2003372253 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12907620
TITLE: Rapamycin inhibits the interleukin 10 signal transduction pathway and the growth of Epstein Barr virus B-cell lymphomas.
AUTHOR: Nepomuceno Ronald R; Balatoni Cynthia E; Natkunam Yaso; Snow Andrew L; Krams Sheri M; Martinez Olivia M
CORPORATE SOURCE: Department of Surgery, Stanford University School of Medicine, 1201 Welch Road, Stanford, CA 94305, USA.
CONTRACT NUMBER: R01 AI 41769 (NIAID)
SOURCE: Cancer research, **(2003 Aug 1)** 63 (15) 4472-80. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030809
Last Updated on STN: 20030924
Entered Medline: 20030923

AB EBV-infected B-cell lymphomas are a potentially life-threatening complication in bone marrow and solid organ transplant recipients. Immunosuppressive drugs required to prevent allograft rejection also impair anti-EBV T-cell immunity, thereby increasing the risk of EBV-associated disease. Here we demonstrate that the immunosuppressant rapamycin (RAPA) has a strong antiproliferative effect in vitro on B-cell lines derived from organ transplant recipients with EBV-associated posttransplant lymphoproliferative disorder (PTLD). Furthermore, RAPA significantly inhibits or delays the growth of solid tumors established from EBV-infected B-cell lines in a xenogeneic mouse model of PTLD. RAPA acts via cell cycle arrest, induction of apoptosis, and, most importantly,

inhibition of interleukin 10 secretion, a necessary autocrine growth factor. The reduced interleukin 10 production is accompanied by corresponding decreases in the constitutive activation of the growth-promoting transcription factors signal transducer and activator of transcription 1 and 3. Thus, RAPA can limit B-cell lymphoma growth while simultaneously providing immunosuppression to prevent graft rejection in patients who are otherwise at risk for EBV-associated PTLD. Moreover, these findings may have application to other EBV-associated malignancies.

L20 ANSWER 5 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2003332788 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12864941
TITLE: Mammalian target of rapamycin: a new molecular target for breast cancer.
AUTHOR: Mita Monica M; Mita Alain; Rowinsky Eric K
CORPORATE SOURCE: Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, TX, USA.. mmita@idd.org
SOURCE: Clinical breast cancer, **(2003 Jun)** 4 (2) 126-37.
Ref: 148
Journal code: 100898731. ISSN: 1526-8209.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20030717
Last Updated on STN: 20031107
Entered Medline: 20031106

AB The mammalian target of rapamycin (mTOR), a downstream effector of the phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B) signaling pathway that mediates cell survival and proliferation, is a prime strategic target for anticancer therapeutic development. By targeting mTOR, the immunosuppressant and antiproliferative agent rapamycin inhibits signals required for cell cycle progression, cell growth, and proliferation. Both rapamycin and novel rapamycin analogues with more favorable pharmaceutical properties, such as CCI-779, RAD 001, and AP23573, are highly specific inhibitors of mTOR. In essence, these agents gain function by binding to the immunophilin FK506 binding protein 12 and the resultant complex inhibits the activity of mTOR. Because mTOR activates both the 40S ribosomal protein S6 kinase (p70s6k) and the eukaryotic initiation factor 4E-binding protein-1, rapamycin-like compounds block the actions of these downstream signaling elements, which results in cell cycle arrest in the G1 phase. Rapamycin and its analogues also prevent cyclin-dependent kinase (CDK) activation, inhibit retinoblastoma protein phosphorylation, and accelerate the turnover of cyclin D1, leading to a deficiency of active CDK4/cyclin D1 complexes, all of which potentially contribute to the prominent inhibitory effects of rapamycin at the G1/S boundary of the cell cycle. Rapamycin and rapamycin analogues have demonstrated impressive growth-inhibitory effects against a broad range of human cancers, including breast cancer, in preclinical and early clinical evaluations. In breast cancer cells, PI3K/Akt and mTOR pathways seem to be critical for the proliferative responses mediated by the epidermal growth factor receptor, the insulin growth factor receptor, and the estrogen receptor. Furthermore, these pathways may be constitutively activated in cancers with many types of aberrations, including those with loss of PTEN suppressor gene function. Therefore, the development of inhibitors of mTOR and related pathways is a rational

therapeutic strategy for breast and other malignancies that possess a wide range of aberrant molecular constituents. This review will summarize the principal mechanisms of action of rapamycin and rapamycin derivatives, as well as the potential utility of these agents as anticancer therapeutic agents with an emphasis on breast cancer. The preliminary results of early clinical evaluations with rapamycin analogues and the unique developmental challenges that lie ahead will also be discussed.

L20 ANSWER 6 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2003116996 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12630766
TITLE: The preventive effect of ketoconazole on experimental metastasis from a human pancreatic carcinoma may be related to its effect on prostaglandin synthesis.
AUTHOR: Tzanakakis George N; Krambovitis Elias; Tsatsakis Aristidis M; Vezeridis Michael P
CORPORATE SOURCE: Department of Histology, School of Medicine, University of Crete, Heraklion, Greece.. tzanakak@med.uoc.gr
CONTRACT NUMBER: CA 07340 (NCI)
SOURCE: International journal of gastrointestinal cancer, **(2002)** 32 (1) 23-30.
Journal code: 101135379. ISSN: 1537-3649.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030313
Last Updated on STN: 20030528
Entered Medline: 20030527

AB BACKGROUND: Arachidonic acid metabolites known to affect platelet function also interfere with tumor growth and metastases. The purpose of this study was to evaluate the anti-metastatic potential of ketoconazole, a thromboxane synthetase and 5-lipoxygenase inhibitor, on hepatic metastasis from a human pancreatic adenocarcinoma in nude mice and its effect on serum prostaglandin levels. METHODS: The human pancreatic tumor cells (RWP-2) were injected intrasplenically in nude mice grouped into control, ketoconazole (270 microg), ketoconazole (360 microg), and ketoconazole (540 microg). The agent was administered intraperitoneally 30 min before and every 24 h after the tumor cell inoculation for 8 days. In a separate experiment thromboxane B2 (TxB2), prostaglandin D2 (PGD2), prostaglandin E2 (PGE2) and 6-Keto-F1a (stable prostacyclin derivative) were measured on blood from controls, tumor bearing animals and animals bearing tumors treated with 270 microg of ketoconazole. RESULTS: Statistically significant differences were observed between the control and three-treatment groups on the reduction of liver tumor nodules ($p < 0.001$), and in the liver surface areas occupied by tumor ($p < 0.001$). The TxB2 levels decreased from 150.6 ng/mL in the tumor bearing to 104.8 ng/mL in the ketoconazole treated animals ($p < 0.05$). PGD2, PGE2 and 6-keto-F1a levels increased to 7.1 ng/mL, 8.3 ng/mL, and 13.6 ng/mL from 3 ng/mL, 5.8 ng/mL, and 0.02 ng/mL respectively ($p < 0.001$). CONCLUSIONS: These results indicate that ketoconazole significantly reduced hepatic metastases from the human pancreatic carcinoma RWP-2 in the nude mouse model, and inhibited thromboxane B2 formation, potentiating a concomitant redirection of platelet endoperoxide metabolism into PGD2, PGE2, and 6-keto-F1a. It is hypothesized that the changes in the arachidonic acid metabolism mediate the ameliorating effect of ketoconazole on experimental hepatic metastasis.

L20 ANSWER 7 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2003024014 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12530001
TITLE: The combined effects of antibacterial peptide cecropin A and anti-cancer agents on leukemia cells.
AUTHOR: Hui Ling; Leung Keith; Chen Hueih Min
CORPORATE SOURCE: Institute of Bio Agricultural Sciences, Academia Sinica, Taipei, Taiwan.
SOURCE: Anticancer research, **(2002 Sep-Oct)** 22 (5) 2811-6.
Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20030118
Last Updated on STN: 20030221
Entered Medline: 20030220

AB Anti-microbial cecropins are humoral immune peptides originally found in insects. They possess a particular function of membrane permeabilization on both gram-positive and gram-negative bacteria. Yet, they are not capable of lysing eucaryotic cells. In this experiment, we confirmed that cecropin A (CA) is a special agent able to lyse leukemia cells while exerting little toxic effect on normal lymphocytes, based on the IC50 measurements. The therapeutic index of CA ranged from 6 to 17. In contrast, chemical anti-cancer agents (ACAs) are non-specific drugs capable of damaging both cancer and normal cells. Due to the functional differences between CA and ACAs, the experiments on the combined effects of CA and ACAs were conducted in vitro. Under certain conditions, synergistic effects were found with CA/S-FU and CA/Ara-C combinations. The results suggest the need for further study into the possible application of combining anti-cancer agents with antibacterial peptides for cancer treatment.

L20 ANSWER 8 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2002654029 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12414639
TITLE: Inhibitors of mTOR reverse doxorubicin resistance conferred by PTEN status in prostate cancer cells.
AUTHOR: Grunwald Viktor; DeGraffenried Linda; Russel Douglas; Friedrichs William E; Ray Ratna B; Hidalgo Manuel
CORPORATE SOURCE: The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland 21231, USA.
CONTRACT NUMBER: R25 CA80946 (NCI)
SOURCE: Cancer research, **(2002 Nov 1)** 62 (21) 6141-5.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021105
Last Updated on STN: 20021217
Entered Medline: 20021210

AB Phosphatase and tensin homologue deleted from chromosome 10 (PTEN) is a lipid phosphatase with putative tumor suppressing abilities, which is frequently mutated in prostate cancer. Loss of PTEN leads to constitutive activation of the phosphatidylinositol 3'-kinase/serine-threonine kinase

(Akt) signal transduction pathway and has been associated with resistance to chemotherapy. This study aimed to determine the effects of PTEN status and treatment with rapamycin, an inhibitor of mTOR, in the response of prostate cancer cell lines to doxorubicin. The DU-145 PTEN-positive cell line was significantly more susceptible to the antiproliferative effects of doxorubicin as compared with the PTEN-negative PC-3 cell line. Transfection of PTEN into the PC3 cells decreased the activation of Akt and the downstream mTOR-regulated 70-kDa S6 (p70(s6k)) kinase and reversed the resistance to doxorubicin in these cells, indicating that changes in PTEN status/Akt activation modulate the cellular response to doxorubicin. Treatment of PC-3 PTEN-negative cells with rapamycin inhibited 70-kDa S6 kinase and increased the proliferative response of these cells to doxorubicin, so that it was comparable with the responses of PTEN-positive DU-145 cells and the PC-3-transfected cells. Furthermore, treatment of mice bearing the PTEN-negative PC-3 prostate cancer xenografts with CCI-779, an ester of rapamycin in clinical development combined with doxorubicin, inhibited the growth of the doxorubicin-resistant PC-3 tumors confirming the observations in vitro. Thus, rapamycin and CCI-779, by interacting with downstream intermediates in the phosphatidylinositol 3'-kinase/Akt signaling pathway, reverse the resistance to doxorubicin conferred by PTEN mutation/Akt activation. These results provide the rationale to explore in clinical trials whether these agents increase the response to chemotherapy of patients with PTEN-negative/Akt active cancers.

L20 ANSWER 9 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2002451882 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12211424
TITLE: CCI-779 Wyeth.
AUTHOR: Elit Laurie
CORPORATE SOURCE: Hamilton Regional Cancer Center, Ontario, Canada.. laurie.elit@hrcc.on.ca
SOURCE: Current opinion in investigational drugs (London, England : 2000), **(2002 Aug)** 3 (8) 1249-53. Ref: 38
Journal code: 100965718. ISSN: 1472-4472.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20020906
Last Updated on STN: 20030319
Entered Medline: 20030318

AB Wyeth Research (formerly Wyeth-Ayerst Research) is developing the sirolimus (rapamycin) analog CCI-779 as a potential treatment for various cancers [320924]. By November 2001, phase III trials had been initiated [428972], [429576]. In October 2001, Raymond James predicted filing in 2003, with a potential launch in 2005 [426718]. In March 2002, CCI-779, was designated for fast-track development by the FDA for the treatment of renal cell carcinoma after failure of initial therapy [442535]; at this time phase III trials for renal cell carcinoma and phase II trials for various solid tumors were ongoing [444030]. In March 2002, Wyeth revealed that filing was anticipated for 2004/2005 [443491]. In June and August 2001, Lehman Brothers predicted sales of US $40 million ($20 million in the US) in 2003, rising to US $75 million ($38 million in the US) in 2004 [418901], [420809]. In October 2001, analysts at Raymond James expected potential sales of the product at US $250 million [426718]. In May 2002,

a patent (WO-00240000) was published claiming CCI-779 to be useful for the treatment of cancers of various origins, including renal, breast, cervical, uterine, head and neck, lung, prostate, pancreatic, ovarian, colon, lymphoma and melanoma.

L20 ANSWER 10 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2002389325 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12137719
TITLE: Interventions for preventing oral candidiasis for patients with cancer receiving treatment.
COMMENT: Comment in: ACP J Club. 2003 Mar-Apr;138(2):46. PubMed ID: 12614131
Update in: Cochrane Database Syst Rev. 2004;(4):CD003807. PubMed ID: 15495065
AUTHOR: Worthington H V; Clarkson J E; Eden O B
CORPORATE SOURCE: Oral Health and Development, University Dental Hospital of Manchester, Higher Cambridge Street, Manchester, UK, M15 6FH.. helen.worthington@man.ac.uk
SOURCE: Cochrane database of systematic reviews (Online : Update Software), **(2002)** (3) CD003807. Ref: 64
Journal code: 100909747. ISSN: 1469-493X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(META-ANALYSIS)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020725
Last Updated on STN: 20030326
Entered Medline: 20020924

AB BACKGROUND: Treatment of cancer is increasingly more effective but is associated with short and long-term side effects. Oral side effects remain a major source of illness despite the use of a variety of agents to prevent and treat them. One of these side effects is oral candidiasis. OBJECTIVES: To assess the effectiveness of interventions (which may include placebo or no treatment) for the prevention of oral candidiasis for patients with cancer receiving chemotherapy and or radiotherapy. SEARCH STRATEGY: Electronic databases : Cochrane Oral Health Group Specialised Register, CCTR, MEDLINE and EMBASE were searched. Date of the most recent searches May 2001 (CCTR 2001, issue 3). SELECTION CRITERIA: Trials were selected if they met the following criteria: design - random allocation of participants; participants - anyone receiving chemotherapy or radiotherapy treatment for cancer; interventions - agents prescribed to prevent oral candidiasis; primary outcome - prevention of oral candidiasis. DATA COLLECTION AND ANALYSIS: Data were recorded on the following secondary outcomes if present: relief of pain, amount of analgesia, relief of dysphagia, incidence of systemic infection, duration of stay in hospital (days), cost of oral care, patient quality of life, death, use of empirical antifungal treatment, toxicity and compliance. Information regarding methods, participants, interventions, outcome measures and results were independently extracted, in duplicate, by two reviewers (HW & JC). The Cochrane Oral Health Group statistical guidelines were followed and relative risk values calculated using random effects models where significant heterogeneity was detected ($P<0.1$). Potential sources of heterogeneity were examined in random effects meta-regression analyses. MAIN RESULTS: Twenty-seven trials involving 4,137 patients satisfied the inclusion criteria. Drugs absorbed and partially absorbed from the GI tract were found to prevent oral

candidiasis when compared to a placebo, or a no treatment control group, with RR for absorbed drugs =0.45 (95%CI 0.31 to 0.64). For absorbed drugs in populations with an incidence of 20% (mid range of results in control groups), this implies a NNT of 9 (95%CI 7 to 13) patients need to be treated to avoid one patient getting oral candidiasis. There was no significant benefit for drugs not absorbed from the GI tract. REVIEWER'S CONCLUSIONS: There is strong evidence, from randomised controlled trials, that drugs absorbed or partially absorbed from the GI tract prevent oral candidiasis in patient receiving treatment for cancer. There is also evidence that these drugs are significantly better at preventing oral candidiasis than drugs not absorbed from the GI.

L20 ANSWER 11 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2002368160 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12115356
TITLE: Antifungal prophylaxis for severely neutropenic chemotherapy recipients: a meta analysis of randomized-controlled clinical trials.
AUTHOR: Bow Eric J; Laverdiere Michel; Lussier Nathalie; Rotstein Coleman; Cheang Mary S; Ioannou Stratis
CORPORATE SOURCE: Department of Internal Medicine, the University of Manitoba and CancerCare Manitoba, Winnipeg, Manitoba, Canada.. ebow@hsc.mb.ca
SOURCE: Cancer, **(2002 Jun 15)** 94 (12) 3230-46.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (META-ANALYSIS)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020713
Last Updated on STN: 20020801
Entered Medline: 20020731

AB BACKGROUND: The overall clinical efficacy of the azoles antifungal agents and low-dose intravenous amphotericin B for antifungal chemoprophylaxis in patients with malignant disease who have severe neutropenia remains unclear. METHODS: Randomized-controlled trials of azoles (fluconazole, itraconazole, ketoconazole, and miconazole) or intravenous amphotericin B formulations compared with placebo/no treatment or polyene-based controls in severely neutropenic chemotherapy recipients were evaluated using meta-analytical techniques. RESULTS: Thirty-eight trials that included 7014 patients (study agents, 3515 patients; control patients, 3499 patients) were analyzed. Overall, there were reductions in the use of parenteral antifungal therapy (prophylaxis success: odds ratio [OR], 0.57; 95% confidence interval [95% CI], 0.48-0.68; relative risk reduction [RRR], 19%; number requiring treatment for this outcome [NNT], 10 patients), superficial fungal infection (OR, 0.29; 95% CI, 0.20-0.43; RRR, 61%; NNT, 12 patients), invasive fungal infection (OR, 0.44; 95% CI, 0.35-0.55; RRR, 56%; NNT, 22 patients), and fungal infection-related mortality (OR, 0.58; 95% CI, 0.41-0.82; RRR, 47%; NNT, 52 patients). Invasive aspergillosis was unaffected (OR, 1.03; 95% CI, 0.62-1.44). Although overall mortality was not reduced (OR, 0.87; 95% CI, 0.74-1.03), subgroup analyses showed reduced mortality in studies of patients who had prolonged neutropenia (OR, 0.72; 95% CI, 0.55-0.95) or who underwent hematopoietic stem cell transplantation (HSCT) (OR, 0.77; 95% CI, 0.59-0.99). The multivariate metaregression analyses identified HSCT, prolonged neutropenia, acute leukemia with prolonged neutropenia, and higher azole dose as predictors of treatment effect. CONCLUSIONS:

Antifungal prophylaxis reduced morbidity, as evidenced by reductions in the use of parenteral antifungal therapy, superficial fungal infection, and invasive fungal infection, as well as reducing fungal infection-related mortality. These effects were most pronounced in patients with malignant disease who had prolonged neutropenia and HSCT recipients.

L20 ANSWER 12 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2002278065 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12020063
TITLE: Inhibitors of mammalian target of rapamycin as novel antitumor agents: from bench to clinic.
AUTHOR: Huang Shile; Houghton Peter J
CORPORATE SOURCE: Department of Molecular Pharmacology, St Jude Children's Research Hospital, Memphis, TN 38105-2794, USA.
CONTRACT NUMBER: CA23099 (NCI)
CA28765 (NCI)
CA77776 (NCI)
SOURCE: Current opinion in investigational drugs (London, England : 2000), **(2002 Feb)** 3 (2) 295-304. Ref: 90
Journal code: 100965718. ISSN: 1472-4472.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20020522
Last Updated on STN: 20021218
Entered Medline: 20021217

AB Rapamycin and its derivatives, CCI-779 and RAD-001, inhibit the mammalian target of rapamycin (mTOR), downregulating translation of specific mRNAs required for cell cycle progression from G1 to S phase. Preclinically, mTOR inhibitors potently suppress growth and proliferation of numerous tumor cell lines in culture or when grown in mice as xenografts. CCI-779 and RAD-001 are being developed as antitumor drugs and are undergoing clinical trials. Clinically, CCI-779 has shown evidence of antitumor activity but induced relatively mild side effects in patients. Here we discuss potential antitumor mechanisms and resistance mechanisms of mTOR inhibitors, and summarize the current status of these compounds as novel antitumor agents.

L20 ANSWER 13 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2002190678 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11922774
TITLE: Antitumor effects of miconazole on human colon carcinoma xenografts in nude mice through induction of apoptosis and G0/G1 cell cycle arrest.
AUTHOR: Wu Chih-Hsiung; Jeng Jiiang-Huei; Wang Ying-Jan; Tseng Chia-Jen; Liang Yu-Chih; Chen Chien-Ho; Lee Horng-Mo; Lin Jen-Kun; Lin Chien-Huang; Lin Shyr-Yi; Li Chung-Pei; Ho Yuan-Soon
CORPORATE SOURCE: School of Medicine, Taipei Medical University, Taipei, Taiwan.
SOURCE: Toxicology and applied pharmacology, **(2002 Apr 1)** 180 (1) 22-35.
Journal code: 0416575. ISSN: 0041-008X.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020403
Last Updated on STN: 20020503
Entered Medline: 20020502

AB Miconazole (MIC), a promising oral antifungal agent, has been used worldwide in the treatment of superficial mycosis. In this study, we demonstrated that MIC dose dependently arrested various human cancer cells at the G0/G1 phase of the cell cycle. The protein levels of p53, p21/Cip1, and p27/Kip1 were significantly elevated by MIC treatment in COLO 205 cells. Electrophoretic mobility gel shift assays showed that the nuclear extracts of the MIC-treated COLO 205 cells exerted a significant binding between wild-type p53 and its consensus-binding site present in the p21/Cip1 promoter. These results suggested that the p53-associated signaling pathway is involved in the regulation of MIC-induced cancer cell growth arrest. By immunoblot analysis, we demonstrated that cyclin D3 and cyclin-dependent kinase-4 (CDK4) protein levels were inhibited by MIC treatment in the cancer cells. Significant therapeutic effect was further demonstrated in vivo by treating nude mice bearing COLO 205 tumor xenografts with MIC (50 mg/kg ip). The protein expression of p53 was significantly increased in MIC-treated tumor tissues by immunohistochemical staining and Western blotting analysis. DNA fragmentation and TUNEL assay were performed and demonstrated that apoptosis occurred in tumor tissues treated with MIC. Our study provides the novel mechanisms of antitumor effects of MIC and such results may have significant applications for cancer chemotherapy.

L20 ANSWER 14 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2001519693 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11566616
TITLE: mTOR, a novel target in breast cancer: the effect of CCI-779, an mTOR inhibitor, in preclinical models of breast cancer.
AUTHOR: Yu K; Toral-Barza L; Discafani C; Zhang W G; Skotnicki J; Frost P; Gibbons J J
CORPORATE SOURCE: Wyeth-Ayerst Research, Department of Oncology, 401 North Middletown Road, Pearl River, New York 10965, USA.
SOURCE: Endocrine-related cancer, **(2001 Sep)** 8 (3) 249-58.
Journal code: 9436481. ISSN: 1351-0088.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20010924
Last Updated on STN: 20020122
Entered Medline: 20011205

AB The mammalian target of rapamycin (mTOR) is a central regulator of G1 cell cycle protein synthesis that precedes commitment to normal cellular replication. We have studied the effect of cell cycle inhibitor-779 (CCI-779), a rapamycin ester that inhibits mTOR function, on the proliferation of a panel of breast cancer cell lines. Six of eight lines studied were sensitive (IC(50)< or = 50 nM) and two lines were resistant (IC(50)>1.0 microM) to CCI-779. Sensitive lines were estrogen dependent

(MCF-7, BT-474, T-47D), or lacked expression of the tumor suppressor PTEN (MDA-MB-468, BT-549), and/or overexpressed the Her-2/neu oncogene (SKBR-3, BT-474). Resistant lines (MDA-MB-435, MDA-MB-231) shared none of these properties. CCI-779 (50 nM) inhibited mTOR function in both a sensitive and a resistant line. In nu/nu mouse xenografts, CCI-779 inhibited growth of MDA-MB-468 (sensitive) but not MDA-MB-435 resistant tumors. Treatment of sensitive lines with CCI-779 resulted in a decrease in D-type cyclin and c-myc levels and an increase in p27(kip-1) levels. There was good correlation between activation of the Akt pathway and sensitivity to CCI-779. Amplification of mTOR-regulated p70S6 kinase, which is downstream of Akt, may also have conferred CCI-779 sensitivity to MCF-7 cells. Taken together, the data suggest that mTOR may be a good target for breast cancer therapy, especially in tumors with Akt activation resulting from either growth factor dependency or loss of PTEN function.

L20 ANSWER 15 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2001279617 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11363009
TITLE: Early approval for two lipid-based drugs.
AUTHOR: Baker R
SOURCE: BETA bulletin of experimental treatments for AIDS : a publication of the San Francisco AIDS foundation, **(1995 Dec)** 4.
Journal code: 9113964. ISSN: 1058-708X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (NEWSPAPER ARTICLE)
LANGUAGE: English
FILE SEGMENT: AIDS
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 20010529
Last Updated on STN: 20020222
Entered Medline: 19960118

AB The Food and Drug Administration (FDA) has granted accelerated approval for Doxil (doxorubicin HCl liposome injection) for treatment of AIDS-related Kaposi's sarcoma (KS), and Abelcet (amphotericin B lipid complex) for aspergillosis, a rare but life-threatening fungal illness related to immunosuppression. Sequus, the manufacturer of Doxil, has a patient assistance program for people with KS who might benefit from the drug.

L20 ANSWER 16 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2001209343 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11287445
TITLE: Effects of retinoids on cancerous phenotype and apoptosis in organotypic cultures of ovarian carcinoma.
COMMENT: Comment in: J Natl Cancer Inst. 2001 Apr 4;93(7):486-8.
PubMed ID: 11287432
AUTHOR: Guruswamy S; Lightfoot S; Gold M A; Hassan R; Berlin K D; Ivey R T; Benbrook D M
CORPORATE SOURCE: Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center, Oklahoma City 73190, USA.
SOURCE: Journal of the National Cancer Institute, **(2001 Apr 4)** 93 (7) 516-25.
Journal code: 7503089. ISSN: 0027-8874.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105

ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20030312
Entered Medline: 20010503

AB BACKGROUND: Retinoic acid analogues, called retinoids, have shown promise in clinical trials in preventing breast and ovarian cancers. Classic retinoids bind to retinoic acid receptors, which regulate cell growth. Some novel retinoids, such as fenretinide, i.e., N-(4-hydroxyphenyl)retinamide (4-HPR), induce apoptosis through retinoic acid receptor-independent mechanisms; however, they appear to do so only at concentrations above those achieved in clinical chemoprevention trials. At lower concentrations (< or =1 microM), 4-HPR acts like classic retinoids, by inducing differentiation through a receptor-dependent mechanism. Our goal was to compare the effects of novel receptor-independent (apoptotic) retinoids with those of classic growth-inhibitory retinoids at clinically achievable doses on growth, differentiation, and apoptosis in ovarian tissue. METHODS: Four receptor-independent (apoptotic) and seven growth-inhibitory retinoids, including synthetic, low-toxicity compounds called heteroarotinoids, were administered at concentrations of 1 microM to organotypic cultures of ovarian primary and cancer cell lines: OVCAR-3, Caov-3, and SK-OV-3. After fixation, embedding, and sectioning, the growth fraction was quantified by measuring expression of the proliferation marker Ki-67/myb, differentiation was assessed by expression of mucin, and apoptosis was evaluated by the TUNEL assay. Spearman correlation analysis was performed on the data, and all P values were two-sided. RESULTS: All 11 retinoids reversed characteristics associated with the cancerous phenotype in all neoplastic cultures. Glandular structures were observed consistently in retinoid-treated, but not in untreated, OVCAR-3 and Caov-3 cultures. All retinoids decreased growth fractions, and some increased mucin expression. All receptor-independent retinoids and two receptor-dependent retinoids induced apoptosis, and the induction correlated significantly with increased expression of the mucin MUC1 (r =.83; P =.03). Retinoids with ester-linking groups did not induce apoptosis but decreased the growth fraction in correlation with MUC1 induction (r = -.93; P =.02). CONCLUSIONS: At clinically achievable concentrations, all retinoids tested decrease the growth fraction, induce differentiation and apoptosis. Induction of MUC1 expression is implicated in the mechanisms of action.

L20 ANSWER 17 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2001184211 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11245461
TITLE: Antitumor activity of the rapamycin analog CCI-779 in human primitive neuroectodermal tumor/medulloblastoma models as single agent and in combination chemotherapy.
AUTHOR: Geoerger B; Kerr K; Tang C B; Fung K M; Powell B; Sutton L N; Phillips P C; Janss A J
CORPORATE SOURCE: Division of Neuro-Oncology, Hospital of the University of Pennsylvania, Philadelphia 19104, USA.
CONTRACT NUMBER: POI-NS 34514 (NINDS)
SOURCE: Cancer research, **(2001 Feb 15)** 61 (4) 1527-32.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329

AB We examined the cytotoxicity of the immunosuppressant agent rapamycin and its analogue CCI-779 in human brain tumor cell lines in vitro and in vivo as single agents and in combination with standard chemotherapeutic drugs. In the rapamycin-sensitive PNET/MB cell line DAOY, rapamycin exhibited additive cytotoxicity with cisplatin and with camptothecin. In vivo, CCI-779 delayed DAOY xenograft growth by 160% after 1 week and 240% after 2 weeks of systemic treatment, compared with controls. Single high-dose treatment induced 37% regression of tumor solume. Growth inhibition of DAOY xenografts was 1.3 times greater after simultaneous treatment with CCI-779 and cisplatin than after cisplatin alone. Interestingly, CCI-779 also produced growth inhibition of xenografts derived from U251 malignant glioma cells, a human cell line resistant to rapamycin in vitro. These studies suggest that the rapamycin analogue CCI-779 is an important new agent to investigate in the treatment of human brain tumors, particularly PNET/MB.

L20 ANSWER 18 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2000150750 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10688042
TITLE: Efficacy of microtubule-active drugs followed by ketoconazole in human metastatic prostate cancer cell lines.
AUTHOR: Blagosklonny M V; Dixon S C; Figg W D
CORPORATE SOURCE: Medicine Branch, Division of Clinical Sciences, National Cancer Institute, NIH, Bethesda, Maryland 20892, USA.
SOURCE: Journal of urology, **(2000 Mar)** 163 (3) 1022-6.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000316

AB PURPOSE: Once a relapse occurs following primary endocrine treatment, metastatic prostate cancer is one of the most therapy-resistant human neoplasms. Ketoconazole is used for complete androgen deprivation, and recent data suggest it has direct activity against prostate cancer cells. MATERIALS AND METHODS: LNCaP, DU145, and PC3 cells, human prostate cancer cell lines, and HL60, a human leukemia cell line, were lysed and soluble proteins were harvested. Cells were plated in 96-well flat bottom plates and then exposed to the pharmacological agents, ketoconazole, vinblastine and paclitaxel. DNA synthesis was monitored by 3H-thymidine incorporation. RESULTS: We demonstrate that ketoconazole exerts a cytostatic effect on a panel of human prostate cancer cell lines, with IC50 of 4 to 5 microg./ml., 12 microg./ml., and 25 microg./ml. for LNCaP, PC3/PC3M, and DU145 cells, respectively. On the other hand, using microtubule-active drugs, vinblastine and paclitaxel, we found that PC3M and PC3 cells were more resistant than either DU145 or LNCaP cells. This resistance was associated with a lesser degree of Raf-1 and Bcl-2 phosphorylation following exposure to microtubule-active drugs. Combinations of microtubule-active drugs with ketoconazole were a beneficial treatment in DU145 cancer cells. Furthermore, ketoconazole blocked recovery of all the prostate cancer cell lines following 24 hours-pulse treatment with vinblastine. CONCLUSION: Pulse-administration of vinblastine followed by continuous administration of ketoconazole warrants investigation in the treatment of hormone-independent metastatic prostate cancer.

L20 ANSWER 19 OF 50 MEDLINE on STN
ACCESSION NUMBER: 2000086250 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10622538
TITLE: TAC-101 (4-[3,5-bis(trimethylsilyl)benzamido]benzoic acid) inhibits spontaneous mediastinal lymph node metastasis produced by orthotopic implantation of Lewis lung carcinoma.
AUTHOR: Murakami K; Yamaura T; Suda K; Ohie S; Shibata J; Toko T; Yamada Y; Saiki I
CORPORATE SOURCE: Department of Pathogenic Biochemistry, Institute of Natural Medicine, Toyama Medical and Pharmaceutical University.. komuraka@hanno.taiho.co.jp
SOURCE: Japanese journal of cancer research : Gann, **(1999 Nov)** 90 (11) 1254-61.
Journal code: 8509412. ISSN: 0910-5050.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000114
Last Updated on STN: 20000114
Entered Medline: 20000106

AB The anti-tumor and anti-metastatic effects of 4-[3,5-bis(trimethylsilyl)benzamido]benzoic acid (TAC-101) were investigated using our established lung cancer model. Orthotopic implantation of Lewis lung carcinoma (LLC) cells into the lung parenchyma produced a solitary tumor nodule in the lung followed by mediastinal lymph node metastasis. Daily oral administration of TAC-101 at doses ranging from 4 to 16 mg/kg resulted in a significant inhibition of lymphatic metastasis (inhibition rate=57 to 76%), while only the dose of 16 mg/kg significantly inhibited tumor growth at the implanted sites (inhibition rate=46%). Combined treatment with cis-diamminedichloroplatinum (CDDP) and TAC-101 (8 mg/kg, p.o., daily) enhanced the anti-tumor effect of CDDP (7 mg/kg, i.v., bolus) against both the growth of implanted tumor and lymphatic metastasis. In addition, this combined treatment significantly prolonged the survival time of LLC tumor-bearing mice as compared to treatment with each agent alone. The anti-activating protein-1 (AP-1) activity of TAC-101 caused inhibition of LLC cell invasion through the repression of expression of urokinase-type plasminogen activator and its receptor. The anti-invasive activity of TAC-101 may be involved in its in vivo anti-metastatic activity. These findings suggest that TAC-101 is a novel anti-cancer agent that may improve the therapeutic modalities for lung cancer patients with metastatic disease.

L20 ANSWER 20 OF 50 MEDLINE on STN
ACCESSION NUMBER: 1999021716 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9804616
TITLE: Studies on the mechanism of resistance to rapamycin in human cancer cells.
AUTHOR: Hosoi H; Dilling M B; Liu L N; Danks M K; Shikata T; Sekulic A; Abraham R T; Lawrence J C Jr; Houghton P J
CORPORATE SOURCE: Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, USA.
CONTRACT NUMBER: 5T32CA09346 (NCI)
CA21675 (NCI)
CA23099 (NCI)
SOURCE: Molecular pharmacology, **(1998 Nov)** 54 (5) 815-24.

Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981216

AB Rapamycin is a potent cytostatic agent that arrests cells in the G1 phase of the cell cycle. The relationships between cellular sensitivity to rapamycin, drug accumulation, expression of mammalian target of rapamycin (mTOR), and inhibition of growth factor activation of ribosomal p70S6 kinase (p70(S6k)) and dephosphorylation of pH acid stable protein I (eukaryotic initiation factor 4E binding protein) were examined. We show that some cell lines derived from childhood tumors are highly sensitive to growth inhibition by rapamycin, whereas others have high intrinsic resistance (>1000-fold). Accumulation and retention of [14C]rapamycin were similar in sensitive and resistant cells, with all cells examined demonstrating a stable tight binding component. Western analysis showed levels of mTOR were similar in each cell line (<2-fold variation). The activity of p70(S6k), activated downstream of mTOR, was similar in four cell lines (range, 11.75-41. 8 pmol/2 x 10(6) cells/30 min), but activity was equally inhibited in cells that were highly resistant to rapamycin-induced growth arrest. Rapamycin equally inhibited serum-induced phosphorylation of pH acid stable protein I in Rh1 (intrinsically resistant) and sensitive Rh30 cells. In serum-fasted Rh30 and Rh1 cells, the addition of serum rapidly induced c-MYC (protein) levels. Rapamycin blocked induction in Rh30 cells but not in Rh1 cells. Serum-fasted Rh30/rapa10K cells, selected for high level acquired resistance to rapamycin, showed >/=10-fold increased c-MYC compared with Rh30. These results suggest that the ability of rapamycin to inhibit c-MYC induction correlates with intrinsic sensitivity, whereas failure of rapamycin to inhibit induction or overexpression of c-MYC correlates with intrinsic and acquired resistance, respectively.

L20 ANSWER 21 OF 50 MEDLINE on STN
ACCESSION NUMBER: 1998080191 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9420024
TITLE: Trimetrexate: experience with solid tumors.
AUTHOR: Haller D G
CORPORATE SOURCE: Department of Medicine, University of Pennsylvania Cancer Center, The University of Pennsylvania School of Medicine, Philadelphia 19104, USA.
SOURCE: Seminars in oncology, **(1997 Oct)** 24 (5 Suppl 18) S18-71-S18-76. Ref: 28
Journal code: 0420432. ISSN: 0093-7754.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980114

AB Trimetrexate (TMTX), a potent inhibitor of the enzyme dihydrofolate reductase, is biochemically and metabolically similar to methotrexate

(MTX). Fundamental differences between TMTX and MTX, however, mandate investigation of TMTX in both MTX-sensitive and MTX-resistant tumors. In a number of phase II clinical trials, the antitumor activity of single-agent TMTX has been variable, in part because of the heterogeneity of doses and schedules used and in part because of diverse patient populations. Single-agent activity has been documented in some commonly occurring tumors, including breast, non-small cell lung, and head and neck cancers. Other tumors with sensitivity to single-agent TMTX include transitional cell carcinomas of the urothelium, prostate cancer, and gastric carcinoma. In a small series of children with renal cell carcinoma, significant clinical activity was suggested. The single-agent activity of TMTX, coupled with the finding that TMTX may act as a biochemical modulator of 5-fluorouracil/leucovorin, suggests that the addition of TMTX to 5-fluorouracil/leucovorin should be investigated further. The possibility that TMTX may both exhibit single-agent activity and modulate the effectiveness of other agents makes combination therapy attractive.

L20 ANSWER 22 OF 50 MEDLINE on STN
ACCESSION NUMBER: 1998080189 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9420022
TITLE: Trimetrexate: review and current clinical experience in advanced colorectal cancer.
AUTHOR: Blanke C D; Messenger M; Taplin S C
CORPORATE SOURCE: Department of Medicine, The Vanderbilt Cancer Center, Nashville, TN, USA.
SOURCE: Seminars in oncology, **(1997 Oct)** 24 (5 Suppl 18) S18-57-S18-63. Ref: 42
Journal code: 0420432. ISSN: 0093-7754.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980114

AB Unresectable metastatic colorectal cancer remains a significant cause of morbidity and mortality in both the United States and Europe. To date, no chemotherapeutic regimen for this disease has demonstrated a definitive survival advantage compared with 5-fluorouracil (5-FU) plus leucovorin (LV). However, recent trials have raised the possibility that the combination of trimetrexate (TMTX) plus 5-FU/LV may improve response rates and survival in patients with metastatic colorectal cancer. Trimetrexate is a nonclassical antifolate that has demonstrated antitumor activity against a number of malignancies, including those resistant to the classical antifolate methotrexate. While the single-agent activity of TMTX remains modest in metastatic colorectal cancer, the combination of TMTX/5-FU/LV has shown significant activity in several phase II trials. Reported studies include a phase II trial in chemotherapy failures that demonstrated a 20% response rate, and two multicenter phase II trials in previously untreated patients that demonstrated 50% and 38% overall response rates, respectively. Diarrhea was the dose-limiting toxicity in all trials, although a regimen of scheduled loperamide was quite effective in mitigating this complication. These studies are being followed up with two confirmatory phase II studies in chemorefractory patients and two randomized phase III trials comparing TMTX/5-FU/LV with standard 5-FU/LV.

L20 ANSWER 23 OF 50 MEDLINE on STN
ACCESSION NUMBER: 1998080188 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9420021
TITLE: Biomodulation of 5-fluorouracil with antifolates.
AUTHOR: Bertino J R
CORPORATE SOURCE: Program of Molecular Pharmacology and Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.
CONTRACT NUMBER: CA 61586 (NCI)
SOURCE: Seminars in oncology, **(1997 Oct)** 24 (5 Suppl 18) S18-52-S18-56. Ref: 29
Journal code: 0420432. ISSN: 0093-7754.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980114

AB The cytotoxic activity of 5-fluorouracil (5-FU) can be modulated by coadministration of antifolates or leucovorin (LV). Although a recent meta-analysis concluded that a sequential combination of methotrexate (MTX) and 5-FU was superior to 5-FU alone in terms of response rate and survival, combination MTX and 5-FU therapy has not been actively pursued by many leading cancer centers. We have subsequently investigated the combination of trimetrexate (TMTX) plus 5-FU/LV. Unlike MTX, TMTX does not compete with LV for uptake or polyglutamylation. In a phase I clinical study, combination TMTX/5-FU/LV was well tolerated and produced an overall response rate of 20% in previously treated colorectal cancer patients. In a follow-up phase II clinical study, this combination was highly active in patients with advanced colorectal cancer, demonstrating a 50% overall response rate. Currently, a phase III clinical trial is in progress comparing this regimen with combination 5-FU/LV.

L20 ANSWER 24 OF 50 MEDLINE on STN
ACCESSION NUMBER: 97362462 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9218926
TITLE: Cytotoxic activity of cyclosporin A and [3-keto-Bmt1]-[Val2]-cyclosporin (SDZ PSC 833) on tumour cells from patients with haematological malignancies.
AUTHOR: Martinsson P; Nygren P; Fridborg H; Nilsson K; Kristensen J; Larsson R
CORPORATE SOURCE: Department of Clinical Pharmacology, University Hospital, Uppsala University, Sweden.
SOURCE: European journal of clinical pharmacology, **(1997)** 52 (3) 199-203.
Journal code: 1256165. ISSN: 0031-6970.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970908
Last Updated on STN: 19970908
Entered Medline: 19970826

AB OBJECTIVE AND METHOD: The fluorometric microculture cytotoxic assay was employed for characterisation of the cytotoxic effect of cyclosporin A (CsA) and its non-immunosuppressive analogue SDZ PSC 833, [3-keto-Bmt1]-[Val2]-cyclosporin (PSC) in tumour cells from patients with haematological or solid tumours. RESULTS: Tumour cells from patients with chronic lymphocytic leukemia (CLL) or non-Hodgkin's lymphoma (NHL) were found to be more sensitive to both drugs than those of tumour cells from patients with acute lymphocytic leukemia (ALL), acute myoblastic leukaemia (AML) and various solid tumours. There was a close correlation between the effects of the two drugs (correlation coefficient 0.71), but CsA was slightly more active than PSC in most diagnoses. No tumour cells sample showed sensitivity to PSC without also being sensitive to CsA. There was a moderate level of correlation between the activity pattern of CsA and doxorubicin (correlation coefficient 0.66), whereas the correlations with other cytostatics, such as vincristine, cytarabine and melphalan, were low (correlation coefficient -0.11 to 0.33). CONCLUSION: The results indicate that PSC shares the direct cytotoxic properties of CsA, but is slightly less potent. Clinical testing of the cytotoxic effect of these agents in haematological malignancies seems warranted and the apparent non-cross-resistance with standard agents makes cyclosporins a potentially useful adjunct to chemotherapy in those diagnoses.

L20 ANSWER 25 OF 50 MEDLINE on STN
ACCESSION NUMBER: 96046578 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7585511
TITLE: Enzyme/prodrug gene therapy: comparison of cytosine deaminase/5-fluorocytosine versus thymidine kinase/ganciclovir enzyme/prodrug systems in a human colorectal carcinoma cell line.
AUTHOR: Trinh Q T; Austin E A; Murray D M; Knick V C; Huber B E
CORPORATE SOURCE: Division of Cell Biology, Wellcome Research Laboratories, Research Triangle Park, North Carolina 27709, USA.
SOURCE: Cancer research, **(1995 Nov 1)** 55 (21) 4808-12. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951206

AB We have been developing an enzyme/prodrug gene therapy approach for the treatment of primary and metastatic tumors in the liver. This system uses the cytosine deaminase/5-fluorocytosine (CD/5-FCyt) enzyme/prodrug combination. Another system that has received considerable attention is the herpes simplex virus thymidine kinase/ganciclovir (HSV-TK/GCV) enzyme/prodrug combination. The purpose of the present study was to compare these two enzyme/prodrug systems. The human colorectal tumor cell line, WiDr, was genetically modified to express either the CD gene (WiDr/CD) or the HSV-TK gene (WiDr/TK). The IC50 (concentration of drug producing 50% inhibition of cell growth) for GCV was approximately 3.4 microM in WiDr/TK cells, while the IC50 for 5-FCyt was approximately 27 microM in WiDr/CD cells. In vivo antitumor studies were conducted using high but nontoxic levels of GCV (50 mg/kg/day) or 5-FCyt (500 mg/kg/day). When tumor xenografts were composed of 100% of cells expressing either HSV-TK or CD, 100% tumor-free animals were observed after GCV or 5-FCyt treatment, respectively. However, when only 10% of the tumor cells expressed HSV-TK, no antitumor effect by GCV treatment could be observed.

In contrast, when tumors were composed of 4% of the cells expressing CD, 60% of the animals were tumor-free after 5-FCyt treatment. Transmission electron microscopy of the WiDr solid tumors revealed the presence of desmosomes but no gap junctions.

L20 ANSWER 26 OF 50 MEDLINE on STN
ACCESSION NUMBER: 95007556 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7923167
TITLE: Effects of amiodarone, cyclosporin A, and PSC 833 on the cytotoxicity of mitoxantrone, doxorubicin, and vincristine in non-P-glycoprotein human small cell lung cancer cell lines.
AUTHOR: van der Graaf W T; de Vries E G; Timmer-Bosscha H; Meersma G J; Mesander G; Vellenga E; Mulder N H
CORPORATE SOURCE: Division of Medical Oncology, University Hospital, Groningen, The Netherlands.
SOURCE: Cancer research, **(1994 Oct 15)** 54 (20) 5368-73.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19970203
Entered Medline: 19941103

AB The multidrug resistance (MDR) modulators amiodarone (AM), cyclosporin A (CsA), and PSC 833 were tested for their potential to modulate cytotoxicity of doxorubicin (DOX), vincristine (VCR), and mitoxantrone (MX) in a sensitive human small cell lung carcinoma cell line GLC4, in its DOX-resistant non-P-glycoprotein subline GLC4-Adr, and in its cisplatin-resistant subline GLC4-CDDP. GLC4-Adr, in which overexpression of the so-called multidrug resistance-associated protein has been demonstrated, is 91-fold resistant for DOX, 22-fold for VCR, and 7.5-fold for MX, compared with its sensitive cell line. AM previously modulated DOX and VCR resistance in the P-glycoprotein-positive human colon cancer cell line COLO 320. Cytotoxicity was studied in the microtiter well tetrazolium assay. In the small cell lung carcinoma cell lines described above, AM did not increase cytotoxicity of DOX, but increased VCR cytotoxicity; moreover, AM was shown to be a potent modulator of MX cytotoxicity. CsA did not potentiate DOX cytotoxicity, but, at a concentration of 4 microM, it modestly increased VCR cytotoxicity in GLC4. However, 0.8 and 4.0 microM CsA protected against MX cytotoxicity in GLC4 and GLC4-CDDP, but no effect was observed in GLC4-Adr. At the much higher ID10 concentration CsA modulated MX cytotoxicity 1.6-fold in GLC4-Adr and slightly in GLC4 and GLC4-CDDP. PSC 833, a nonimmunosuppressive CsA analogue, did not alter the cytotoxicity of DOX or MX in these cell lines, but potentiated VCR cytotoxicity in GLC4-Adr at a concentration of 0.4 microM. The modulation of MX cytotoxicity by AM and the protection by CsA was confirmed in a clonogenic assay. In the colony-forming unit granulocyte-monocyte assay, no additional MX toxicity on normal bone marrow by AM was observed. Flow cytometry of cellular MX fluorescence was performed in order to elucidate the mechanism behind the AM-induced increased MX cytotoxicity. This revealed an increase in cellular MX after 1-h incubation of MX combined with AM and an inhibition of efflux from GLC4 and GLC4-Adr; CsA and PSC 833 had no effect on MX efflux. An increase in MX-induced cleavable complexes by AM in GLC4 was observed using the K+/sodium dodecyl sulfate coprecipitation assay, but no effect of CsA was found. In conclusion, AM enhances MX and VCR cytotoxicity in

these sensitive, non-P-glycoprotein DOX and cisplatin-resistant small cell lung carcinoma cell lines. It also inhibits efflux of MX and causes more MX-induced cleavable complexes.

L20 ANSWER 27 OF 50 MEDLINE on STN
ACCESSION NUMBER: 94299321 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7913083
TITLE: Development of vincristine resistance and increased sensitivity to cyclosporin A and verapamil in the human U-937 lymphoma cell line without overexpression of the 170-kDa P-glycoprotein.
AUTHOR: Botling J; Liminga G; Larsson R; Nygren P; Nilsson K
CORPORATE SOURCE: Department of Pathology, University Hospital, Uppsala University, Sweden.
SOURCE: International journal of cancer. Journal international du cancer, **(1994 Jul 15)** 58 (2) 269-74.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940818
Last Updated on STN: 19970203
Entered Medline: 19940809

AB A vincristine (Vcr)-resistant subline of the human histiocytic lymphoma cell line U-937 (U-937-vcr) has been established and characterized with respect to its phenotypic features, including growth rate, surface marker expression and ability to respond to differentiation-inducing agents. The sensitivity of U-937-vcr cells to the direct cytotoxicity of cyclosporin A (CsA) and verapamil (Ver), and the capacity of these drugs to modify Vcr resistance, were also examined. The U-937-vcr cells exhibited a more than 200-fold resistance to Vcr, and cross-resistance to vinorelbin and taxol. Also, there was a slight cross-resistance to colchicine, doxorubicin and VP16. However, the response of U-937-vcr to CsA or Ver alone was substantially altered, with a marked decrease in their respective IC50s. The U-937-vcr cells did not show increased levels of pgp 170. We conclude that the development of Vcr resistance was not associated with a change in the major phenotypic properties of the U-937 cell line, and that resistance modifier hypersensitivity was not associated with increase in pgp 170 expression.

L20 ANSWER 28 OF 50 MEDLINE on STN
ACCESSION NUMBER: 94288531 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8017855
TITLE: The effects of ketoconazole on the human fibrosarcoma cell line HT-1080.
AUTHOR: Shaughnessey E A; Walker M J; Das Gupta T K
CORPORATE SOURCE: Department of Surgery, City of Hope National Medical Center, Duarte, CA 91010.
CONTRACT NUMBER: PO1 CA31827 (NCI)
T32 CA09432 (NCI)
SOURCE: Anticancer research, **(1994 Mar-Apr)** 14 (2A) 513-6.
Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940810
Last Updated on STN: 19970203
Entered Medline: 19940725

AB In light of the reported cytotoxic effects of the antifungal agent ketoconazole on several malignant cell lines, we investigated the in vitro and in vivo effects of this drug on the human fibrosarcoma cell line HT-1080. Utilizing an anchorage dependent in vitro assay, we demonstrated an IC90 of 10.0 micrograms/ml at 72 hours and a decreasing IC90 with increasing exposure (IC90 = 6.2 micrograms/ml at 12 days). In vivo investigation utilizing the subcutaneous growth of this tumor in athymic mice and the oral, subcutaneous or intraperitoneal administration of ketoconazole at doses of 5-50 mg/kg/day demonstrated no consistent activity. Ketoconazole appears to have significant in vitro activity for HT-1080 but this does not translate into significant in vivo activity and its clinical relevance in sarcoma remains uncertain.

L20 ANSWER 29 OF 50 MEDLINE on STN
ACCESSION NUMBER: 94252015 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8194282
TITLE: Clinical pharmacokinetics and pharmacology of trimetrexate.
AUTHOR: Marshall J L; DeLap R J
CORPORATE SOURCE: Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, DC.
SOURCE: Clinical pharmacokinetics, **(1994 Mar)** 26 (3) 190-200. Ref: 61
Journal code: 7606849. ISSN: 0312-5963.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940707
Last Updated on STN: 19940707
Entered Medline: 19940624

AB Trimetrexate represents one of a number of new antimetabolites that have been studied in malignant, rheumatological and infectious disease. Methotrexate, the classical antifolate agent, is active in a broad spectrum of clinical settings, but its use is limited ny pre-existing or acquired cellular resistance. Trimetrexate is an agent that does not require uptake by the folate carrier transport system, a major mechanism of cellular resistance both in vitro and in vivo. Both dihydrofolate reductase inhibition and high performance liquid chromatography (HPLC) assays can be used to determine drug concentrations. Clearance of trimetrexate has been reported to follow biphasic or triphasic patterns. Elimination is primarily by biotransformation with less than 5% of the drug excreted renally in an unchanged form. Both active and inactive metabolites have been found, but the precise metabolic pathways have yet to be defined. The role of trimetrexate in the treatment of Pneumocystis carinii pneumonia is limited to compassionate use, as clinical studies have shown cotrimoxazole (trimethoprim-sulfamethoxazole) to be superior to trimetrexate. However, in a wide spectrum of malignant processes, trimetrexate appears to have a role either as a high-dose single agent, with calcium folinate (leucovorin calcium) rescue, or in combination with other antineoplastic agents. However, further trials are needed to fully establish the efficacy of trimetrexate in these settings. Increased knowledge of the pattern of resistance for individual tumours and tumour types may result in trimetrexate becoming more widely used clinically.

L20 ANSWER 30 OF 50 MEDLINE on STN
ACCESSION NUMBER: 94171871 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7907333
TITLE: Secondary combined resistance to the multidrug-resistance-reversing activity of cyclosporin A in the cell line F4-6RADR-CsA.
AUTHOR: Dietel M; Herzig I; Reymann A; Brandt I; Schaefer B; Bunge A; Heidebrecht H J; Seidel A
CORPORATE SOURCE: Institut of Pathology, Christian-Albrechts-Universitat zu Kiel, Germany.
SOURCE: Journal of cancer research and clinical oncology, **(1994)** 120 (5) 263-71.
Journal code: 7902060. ISSN: 0171-5216.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940420
Last Updated on STN: 19970203
Entered Medline: 19940412

AB Multidrug-resistant tumor cells can be resensitized by combined application of the selecting cytostatic drug and a chemosensitizer, such as cyclosporin A (CsA) or a calcium channel blocker. Since clinical trials on the circumvention of multidrug resistance (MDR) with chemosensitizers report disparate results, we investigated whether tumor cells of the MDR phenotype can develop additional resistance to the cytostatic chemosensitizer combination. Thus, the Adriamycin(ADR)-selected, P-glycoprotein-positive MDR Friend leukemia cell line F4-6RADR was exposed to stepwise increased concentrations of CsA at a constant level of 0.05 microgram/ml ADR. The initial CsA concentration (plus 0.05 microgram/ml ADR) to inhibit cell growth of F4-6RADR cells by 50% (IC50) was 0.04 microgram/ml. By continuous incubation for more than 6 months, the IC50 for CsA (at constant ADR) was elevated to 3.6 micrograms/ml (90-fold), thus generating the variant F4-6RADR-CsA. The F4-6RADR-CsA cells were cross-resistant for cyclosporin H (CsH), a non-immunosuppressive derivative of CsA. As shown by immunocytochemistry as well as by the polymerase chain reaction and by Western blotting including densitometry, P-glycoprotein was preserved in the F4-6RADR-CsA variant and was expressed at a 4-fold higher level than in F4-6RADR cells. Sodium dodecyl sulfate/polyacrylamide gel electrophoresis analysis could detect no new proteins in F4-6RADR-CsA as compared to F4-6RADR. Interestingly, resistance of F4-6RADR-CsA cells remained reversible for the calcium antagonists verapamil and dihydropyridine B859-35 (dexniguldipine-HCl), indicating that CsA and these compounds interfere with the P glycoprotein function by different pharmacodynamic mechanisms. Transport studies with [14C]ADR, performed in the presence and absence of chemosensitizers, confirmed the good correlation of P-glycoprotein function with the pattern of resistance found in proliferation assays. Cellular accumulation of [3H]cyclosporin was reduced to 71% of that of the F4-6 controls in F4-6RADR-CsA cells, but remained at the level of controls in F4-6RADR cells. Results indicate that increased amounts of the P-glycoprotein--besides other, perhaps more important mechanisms that are as yet unknown--partially mediate CsA resistance in F4-6RADR-CsA cells. We have designated this new form of resistance "secondary combined resistance" (SCR). The results suggest that at least some clinical cases of insensitivity to chemosensitizers or of relapse after reversing therapy could be explained by SCR, and that resensitizing treatment of tumor

patients should be based on the consideration of several chemosensitizers of different pharmacodynamics.

L20 ANSWER 31 OF 50 MEDLINE on STN
ACCESSION NUMBER: 92397869 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1387999
TITLE: Phase II trial for the evaluation of trimetrexate in patients with inoperable squamous carcinoma of the esophagus.
AUTHOR: Falkson G; Ryan L M; Haller D G
CORPORATE SOURCE: Dept. of Medical Oncology, University of Pretoria, Republic of South Africa.
CONTRACT NUMBER: CA 15488 (NCI)
CA 21692 (NCI)
CA 23318 (NCI)
+
SOURCE: American journal of clinical oncology : official publication of the American Radium Society, **(1992 Oct)** 15 (5) 433-5.
Journal code: 8207754. ISSN: 0277-3732.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199210
ENTRY DATE: Entered STN: 19921023
Last Updated on STN: 19921023
Entered Medline: 19921009
AB EST 2287 was a Phase II clinical trial conducted by the Eastern Cooperative Oncology Group (ECOG) designed to evaluate trimetrexate in patients with advanced, measurable, inoperable squamous cell carcinoma of the esophagus. The drug was given at a dose of 12 mg/m2 daily for 5 days every 21 days to patients with carcinoma of the esophagus. The purpose of this study was to evaluate treatment efficacy in terms of tumor response and to assess the toxicity. According to a two-stage stopping rule, the study closed after 15 patients had entered. There were no responses to treatment, and median survival from study entry was 4.3 months. There was one treatment-related death caused by infection. One patient experienced life-threatening hematologic toxicity. Overall severe or worse toxicity occurred in more than half of the patients. It is concluded that additional trials of trimetrexate at this dose and schedule in patients with carcinoma of the esophagus are not warranted.

L20 ANSWER 32 OF 50 MEDLINE on STN
ACCESSION NUMBER: 92299499 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1535065
TITLE: Trimetrexate in advanced renal cell carcinoma. An ECOG phase II trial.
AUTHOR: Witte R S; Elson P; Bryan G T; Trump D L
CORPORATE SOURCE: University of Wisconsin Clinical Cancer Center, Madison.
CONTRACT NUMBER: CA 21076 (NCI)
CA 23318 (NCI)
+
SOURCE: Investigational new drugs, **(1992 Apr)** 10 (1) 51-4.
Journal code: 8309330. ISSN: 0167-6997.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920731
Last Updated on STN: 19920731
Entered Medline: 19920723

AB Thirty-four chemotherapy-naive, ambulatory patients with advanced renal cell cancer were treated with the non-classical antifol trimetrexate at the intravenous dose of 12 mg/m2 daily x 5 every three weeks (8 mg/m2 qd x 5 for greater than 30% bone marrow previously irradiated). One patient experienced a partial response lasting 24 weeks for a response rate of 3% (exact 95% CI, 0.1 to 15.3%). Toxicity was manageable and primarily myelosuppression, gastrointestinal, and mucosal. Trimetrexate has little activity in advanced renal cell carcinoma at this dose and schedule.

L20 ANSWER 33 OF 50 MEDLINE on STN
ACCESSION NUMBER: 92139727 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1779608
TITLE: A sequential immunosuppressive treatment with mizoribin (Bredinin) plus cyclosporin A on the subrenal capsule assay.
AUTHOR: Ushijima K; Nishida T; Oda T; Sugiyama T; Yakushiji M
CORPORATE SOURCE: Department of Obstetrics and Gynecology, National Kokura Hospital, Kitakyushu, Japan.
SOURCE: Kurume medical journal, **(1991)** 38 (3) 195-8.
Journal code: 2985210R. ISSN: 0023-5679.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199203
ENTRY DATE: Entered STN: 19920329
Last Updated on STN: 19920329
Entered Medline: 19920310

AB To minimize immunological interferences on the subrenal capsule (SRC) assay, a new immunosuppressor, mizoribin (MZB: Bredinin) alone or combined with cyclosporin A (ScA) was evaluated by an experimental SRC assay system using a rat ovarian cancer tissue. Daily applications of MZB (200 mg/kg) for 7 days following the xenograft of cancer tissue were insufficient to suppress immunological reactions of the recipient mice, and all the grafted cancer tissues were rejected. Although CsA monotreatment (60 mg/kg of CsA given daily for 7 days) successfully suppressed the host immune reaction, enhanced toxicities of CsA in combination with anticancer agents caused high lethal rate of host mice during the experimental chemotherapy. Sequential use of CsA on day 0 to day 2 followed by MZB on day 3, 5 and 7 brought the most favorable results with minimal host reactions and toxicities. An anticancer screening test using the modified SRCA accurately reflected the results of experimental chemotherapy against the rat ovarian cancer. The immunosuppressive treatment which minimizes immunological interferences with SRC assay chemoscreening test.

L20 ANSWER 34 OF 50 MEDLINE on STN
ACCESSION NUMBER: 90315641 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2369744
TITLE: Potentiation of interleukin 1 alpha mediated antitumor effects by ketoconazole.
AUTHOR: Braunschweiger P G; Kumar N; Constantinidis I; Wehrle J P; Glickson J D; Johnson C S; Furmanski P

CORPORATE SOURCE: Laboratory of Experimental Therapeutics, AMC Cancer Research Center, Denver, Colorado.
CONTRACT NUMBER: CA 33188 (NCI)
CA 48077 (NCI)
CA 49143 (NCI)
+
SOURCE: Cancer research, **(1990 Aug 1)** 50 (15) 4709-17.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199008
ENTRY DATE: Entered STN: 19900921
Last Updated on STN: 19970203
Entered Medline: 19900823

AB In the present studies, the regulatory role of adrenal hormones on the antitumor activity of recombinant human interleukin 1 alpha (IL-1 alpha) was investigated. Ketoconazole, a potent but transient inhibitor of adrenal steroid hormone biosynthesis, inhibited IL-1 alpha induced increases in plasma corticosterone. In s.c. RIF-1 tumors (C3H/HeJ mice) ketoconazole potentiated IL-1 alpha induced hemorrhagic necrosis (59Fe labeled RBC uptake) and prolonged intervals of low tumor perfusion (86Rb+ uptake) and attendant depletion of tumor high energy phosphate reserves as determined by in vivo 31P nuclear magnetic resonance spectroscopy. In normal muscle and skin the ketoconazole-IL-1 alpha combination had no effect on RBC content and little or no effect on tissue perfusion. Ketoconazole potentiation of IL-1 alpha induced tumor pathophysiologies was accompanied by time and ketoconazole dose dependent potentiation of RIF-1 tumor clonogenic cell killing. Although ketoconazole at 40 mg/kg and IL-1 alpha at 25 micrograms/kg alone each produced approximately 50% clonogenic cell kill, a combined treatment (IL-1 alpha 1 h after ketoconazole) resulted in surviving fractions of approximately 1.5%. In vitro, ketoconazole and IL-1 alpha induced only additive clonogenic cell kill in primary RIF-1 explant cultures. The effect of elevated plasma corticosterone levels, induced by ketamine-acepromazine anesthesia, on IL-1 alpha responsiveness was also studied in the RIF-1 tumor model. In C3H/HeJ mice, anesthesia increased plasma corticosterone levels within 30 min, abrogated the IL-1 alpha effect on tumor perfusion, and prevented depletion of tumor high energy phosphate metabolite reserves. Our results are consistent with the hypothesis that IL-1 alpha mediated adrenal hormone responses exert a profound negative feedback on IL-1 alpha antitumor activities. Our data also indicate that adrenal steroid hormone biosynthetic pathways could provide a focus for modulation strategies to increase the efficacy of cytokine based therapeutic interventions.

L20 ANSWER 35 OF 50 MEDLINE on STN

ACCESSION NUMBER: 89354045 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2475237
TITLE: Effects of high-dose ketoconazole on patients who have androgen-independent prostatic cancer.
AUTHOR: Eichenberger T; Trachtenberg J
CORPORATE SOURCE: Department of Surgery, Toronto General Hospital, Ont.
SOURCE: Canadian journal of surgery. Journal canadien de chirurgie, **(1989 Sep)** 32 (5) 349-52.
Journal code: 0372715. ISSN: 0008-428X.
PUB. COUNTRY: Canada
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198910
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19960129
Entered Medline: 19891012

AB Forty-four patients who had metastatic cancer of the prostate that had not responded to conventional hormonal manipulation were treated with high-dose ketoconazole (600 to 1200 mg/d). All had castrate serum concentrations of testosterone prior to therapy. All patients had been categorized as having progressive cancer on assessment by the criteria of the National Prostatic Cancer Project. After treatment with ketoconazole, 57% were recategorized as having stable disease. The majority showed marked subjective lessening of pain on this therapy. Objective responses were noted but were not consistent. Side-effects were common but tolerable. The mean survival time was 73.3 weeks. Ketoconazole may be a useful palliative adjunct in the treatment of hormone-refractory prostatic cancer.

L20 ANSWER 36 OF 50 MEDLINE on STN
ACCESSION NUMBER: 89328485 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2474059
TITLE: High-dose ketoconazole in advanced hormone-refractory prostate cancer: endocrinologic and clinical effects.
AUTHOR: Trump D L; Havlin K H; Messing E M; Cummings K B; Lange P H; Jordan V C
CORPORATE SOURCE: University of Wisconsin Clinical Cancer Center, Madison.
SOURCE: Journal of clinical oncology : official journal of the American Society of Clinical Oncology, **(1989 Aug)** 7 (8) 1093-8.
Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198908
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19960129
Entered Medline: 19890829

AB High-dose ketoconazole (400 mg orally three times a day) and physiologic replacement doses of glucocorticoids (hydrocortisone, 20 mg 8 AM, 10 mg 4 PM, and 8 PM) were administered to 38 patients with advanced prostatic cancer, refractory to at least initial testicular androgen deprivation. Thirty patients were completely evaluable; six were withdrawn due to possible ketoconazole-related toxicity and were considered drug failures. Two patients were unevaluable due to intercurrent therapy or inability to maintain follow-up. Ketoconazole was generally well tolerated. Mild or moderate nausea and vomiting occurred in 37% of patients, but required dose modification or discontinuation in only three patients; no hepatic damage was seen. Five of 36 patients (14%) responded to ketoconazole as determined by palpable or radiographic tumor mass reduction of 50% or greater and normalization of acid phosphatase or bone scan. Fifty percent of patients entered were stable at 90 days. Plasma androstenedione and dehydroepiandrosterone sulfate (DHEAS) were reduced markedly in almost all patients. Plasma testosterone (T) levels were low and remained unchanged, while gonadotropins were persistently elevated. Mean plasma ketoconazole content was 6.6 micrograms/mL after 28 days of therapy. While ketoconazole with hydrocortisone does suppress plasma androgens in advanced prostatic cancer patients, this infrequently causes regression of

cancer that has progressed despite adequate testicular androgen ablation.

L20 ANSWER 37 OF 50 MEDLINE on STN
ACCESSION NUMBER: 89223985 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2652864
TITLE: Ketoconazole high dose in management of hormonally pretreated patients with progressive metastatic prostate cancer. Dutch South-Eastern Urological Cooperative Group.
AUTHOR: Witjes F J; Debruyne F M; Fernandez del Moral P; Geboers A D
CORPORATE SOURCE: Department of Urology, St. Radboudhospital, Catholic University, Nijmegen, The Netherlands.
SOURCE: Urology, **(1989 May)** 33 (5) 411-5.
Journal code: 0366151. ISSN: 0090-4295.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198906
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19990129
Entered Medline: 19890601

AB Ketoconazole high dose (H.D.) effectively reduces the testosterone production in both adrenals and testes. Its use in the management of (metastatic) prostate cancer has been advocated. Even in relapsing patients, after previous hormonal therapy, ketoconazole H.D. could be of value. Twenty-eight relapsing patients, of whom 15 were evaluable at three months, have been treated with ketoconazole H.D. As could be expected, objective response was seen in only a small number of patients followed up till nine months. Subjective improvement, however, was noticed in the majority of symptomatic patients. The side effects and toxicity of the therapy remain a major limitation for the use of ketoconazole, be it as first line treatment or as therapy for relapsing patients.

L20 ANSWER 38 OF 50 MEDLINE on STN
ACCESSION NUMBER: 88004628 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3653189
TITLE: Reversal of cancer chemotherapeutic resistance by amphotericin B--A broad phase I-II pilot study.
AUTHOR: Presant C A; Multhauf P; Metter G
CORPORATE SOURCE: Los Angeles Oncologic Institute, Wilshire Oncology Medical Group, Los Angeles, California 90057.
SOURCE: European journal of cancer & clinical oncology, **(1987 Jun)** 23 (6) 683-7.
Journal code: 8112045. ISSN: 0277-5379.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198710
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19871029

AB In order to determine if it was possible to reverse clinically evident chemotherapeutic drug-resistance, 51 evaluable patients received chemotherapy (in doses and schedules on which they had previously

demonstrated tumor progression) together with amphotericin B (AMB). AMB was given in 1-, 2-, or 4-day courses. There was 1 complete response (2%), and 5 partial responses (10%). Response rates tended to be higher in the 4-day treatment program (23%) than in the 1- or 2-day AMB treatment schedules (8%). Toxicity was that expected with chemotherapy (myelosuppression), or AMB alone (fever, chills, and reversible mild azotemia). We conclude that AMB is only infrequently able to reverse clinical drug-resistance, but that this might have palliative effects in a small number of patients in whom other standard chemotherapeutic drugs lack clinical effectiveness.

L20 ANSWER 39 OF 50 MEDLINE on STN
ACCESSION NUMBER: 87199007 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2437334
TITLE: Long-term experience with high dose ketoconazole therapy in patients with stage D2 prostatic carcinoma.
AUTHOR: Pont A
SOURCE: Journal of urology, **(1987 May)** 137 (5) 902-4.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198706
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19900303
Entered Medline: 19870601

AB The antifungal drug ketoconazole has been shown to block testosterone synthesis. High dose ketoconazole therapy was given to 17 patients with previously untreated stage D2 prostatic cancer. Rapid relief of pain occurred in 15 patients with significant pain. Prostatic acid phosphatase levels normalized or decreased in all patients. Bone scan scores were stable or improved. Two patients remain on therapy for more than 30 months. The remainder have ceased treatment owing to subsequent progressive disease (5 patients), side effects (6) or noncompliance. Eleven patients who had relapse after previous endocrine ablative therapy were treated with ketoconazole. Subjective responses were frequent but long-term objective responses were rare. There was a high incidence of side effects, particularly nausea. Ketoconazole may have limited usefulness as initial therapy in patients with endocrine responsive advanced prostatic cancer. The drug can be palliative in some patients who have failed previous therapeutic modalities. Analogues of the drug should prove to have better efficacy and fewer side effects.

L20 ANSWER 40 OF 50 MEDLINE on STN
ACCESSION NUMBER: 87156165 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2950847
TITLE: Selection of therapeutic agents for intraocular proliferative disease. II. Differing antiproliferative activity of the fluoropyrimidines.
AUTHOR: Blumenkranz M S; Hartzer M K; Hajek A S
CONTRACT NUMBER: EY03934 (NEI)
EY05230 (NEI)
EY06520 (NEI)
SOURCE: Archives of ophthalmology, **(1987 Mar)** 105 (3) 396-9.
Journal code: 7706534. ISSN: 0003-9950.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198704
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19970203
Entered Medline: 19870409

AB We confirm the potent antiproliferative effects of the fluoropyrimidines on cellular proliferation in vitro in three different nonmalignant cell types. All fluoropyrimidines tested, except for fluorocytosine, decrease proliferation of human dermal fibroblasts, bovine aortic vascular endothelial cells, and human retinal pigment epithelial cells in vitro. Fluorouridine, an intracellular metabolite of fluorouracil, is nearly 100-fold more potent than fluorouracil and its deoxymetabolite. Human dermal fibroblasts are more sensitive to the inhibitory effects of deoxymetabolites than the cells of either human retinal pigment epithelium or bovine aortic vascular endothelium. Fluorouridine and other fluoropyrimidines may prove to be valuable second-generation drugs in the treatment of intraocular proliferative disorders.

L20 ANSWER 41 OF 50 MEDLINE on STN
ACCESSION NUMBER: 87046062 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3535491
TITLE: Clotrimazole treatment for prevention of oral candidiasis in patients with acute leukemia undergoing chemotherapy. Results of a double-blind study.
AUTHOR: Cuttner J; Troy K M; Funaro L; Brenden R; Bottone E J
SOURCE: American journal of medicine, **(1986 Nov)** 81 (5) 771-4.
Journal code: 0267200. ISSN: 0002-9343.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198612
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 19950206
Entered Medline: 19861204

AB Fungal infections have become an increasing cause of morbidity in patients with acute leukemia undergoing chemotherapy. Oral candidiasis is prone to develop in these patients, and there is also a risk of the development of esophageal Candida infection. Clotrimazole troches have been previously reported to be effective in the treatment of documented oral Candida infection. This report documents a double-blind controlled study in 30 patients with acute leukemia in which the effectiveness of clotrimazole troches in preventing oropharyngeal candidiasis was assessed. Patients were randomly assigned to receive 10 mg troches of clotrimazole or a placebo three times per day. Mucosal scrapings were obtained weekly and examined directly by smear and culture. There were 28 evaluable patients. Of 12 patients with oral Candida infection, 11 were taking placebo and one received clotrimazole ($p = 0.0002$). Clotrimazole is effective in preventing oropharyngeal candidiasis.

L20 ANSWER 42 OF 50 MEDLINE on STN
ACCESSION NUMBER: 86261884 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3460180
TITLE: Clinical experience with amphotericin B in acute

myelogenous leukemia.
AUTHOR: Stein R S; Greer J P; Ferrin W; Lenox R; Baer M R; Flexner J M
CONTRACT NUMBER: CA 19429 (NCI)
SOURCE: Southern medical journal, **(1986 Jul)** 79 (7) 863-70.
Journal code: 0404522. ISSN: 0038-4348.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198608
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19860814

AB The empirical use of amphotericin B in febrile leukemic patients not responding to antimicrobial agents has previously led to a significant decrease in fatal fungal infections and a significant increase in complete remissions. In this series of 66 patients receiving induction therapy for acute myelogenous leukemia (AML), 49 (74%) received amphotericin B. The median interval between institution of antibiotics and amphotericin B was ten days. Fifteen patients had clinical evidence of fungal infection, but only two (3%) died of fungal infection during induction therapy for AML. We discontinued amphotericin B upon granulocyte recovery (greater than 500/cu mm) unless a pulmonary infiltrate was present. Even though only five of 15 patients with probable fungal infection received more than 1,000 mg of amphotericin B, no patient had recurrent fungal disease while in remission. The incidence of clinically suspected fungal pneumonia during consolidation therapy and reinduction therapy also suggested that our therapy was adequate. An increased incidence of late fungal pneumonia in patients receiving reinduction was associated with prolonged neutropenia (greater than 50 days). This study supports the empirical use of amphotericin B during induction therapy for AML, and suggests that doses can be smaller than those generally recommended for fungal infection.

L20 ANSWER 43 OF 50 MEDLINE on STN
ACCESSION NUMBER: 85244990 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3892729
TITLE: Ketoconazole prophylaxis in patients with solid tumours receiving aggressive immunosuppressive therapy. An open randomized comparison between 200 mg/d and 400 mg/d doses.
AUTHOR: Scrimgeour E; Anderson J D
SOURCE: South African medical journal. Suid-Afrikaanse tydskrif vir geneeskunde, **(1985 Jun 29)** 67 (26) 1044-5.
Journal code: 0404520. ISSN: 0256-9574.
PUB. COUNTRY: South Africa
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198508
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19950206
Entered Medline: 19850801

AB Forty-three patients, most with solid tumours, were included in a study comparing the antifungal prophylactic effect of ketoconazole (Nizoral;

Janssen) 200 mg/d and 400 mg/d during the period of immunosuppressive therapy. Seven patients were not seen for follow-up and 6 died of their underlying disease without clinical evidence of mycosis. Twelve of the patients who could be evaluated received ketoconazole 200 mg/d and 18 received 400 mg/d. No infections occurred during the period of prophylactic treatment. In the group receiving 200 mg/d 10 of 36 cultures (28%) were positive for Candida albicans before prophylaxis. During prophylaxis 5 of 18 cultures (28%) were positive and at the end of the prophylactic regimen 1 out of 37 cultures (3%) was positive. In the 400 mg/d group, 13 of 47 cultures (28%) were positive at the start, 2 out of 20 (10%) were positive during prophylaxis and 1 out of 45 (2%) was still positive at the end. The drug was clinically well tolerated. Twenty of the 30 evaluable patients had no significant biochemical abnormalities, 5 had an increased serum transaminase level, 2 had an increased alkaline phosphatase level, and 3 had combined increases of serum transaminase and alkaline phosphatase levels. These abnormalities are regularly seen in patients with metastatic malignant disease, and are not necessarily related to the ketoconazole prophylaxis.

L20 ANSWER 44 OF 50 MEDLINE on STN
ACCESSION NUMBER: 85151830 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3978637
TITLE: Antineoplastic effects in rats of 5-fluorocytosine in combination with cytosine deaminase capsules.
AUTHOR: Nishiyama T; Kawamura Y; Kawamoto K; Matsumura H; Yamamoto N; Ito T; Ohyama A; Katsuragi T; Sakai T
SOURCE: Cancer research, **(1985 Apr)** 45 (4) 1753-61.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198504
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850429

AB 5-Fluorocytosine (5-FC) lacks antineoplastic activity in human subjects because of the absence of cytosine deaminase (CDase) in mammalian cells. Intratumoral conversion of 5-FC into 5-fluorouracil (5-FUra) by locally implanted capsules containing CDase followed by systemic administration of 5-FC can be expected to induce antineoplastic activity at a local site with minimal systemic toxicity. In vitro and in vivo experiments were performed to evaluate this hypothesis. Spectrophotometric analysis confirmed the deamination of 5-FC to 5-FUra by CDase extracted from cultivated Escherichia coli. In vitro studies showed that 5-FC combined with CDase induced significant growth-inhibitory effects on the cultured glioma cells. An active CDase capsule, made of cellulose tubing, was newly designed for local implantation. 5-FC concentrations in the s.c. tumors of the rats given these CDase capsules, followed by 5-FC administration, showed a sufficient amount of delivery of 5-FC to the tumor tissue. 5-FUra appearing in the tumor reached the level of 8.0 micrograms/g at 2 h and stayed at more than 1.0 microgram/g at between 1 and 6 h. Significant reduction of the tumor growth and cytotoxic changes were observed. The passive cutaneous anaphylaxis reaction demonstrated no allergic reaction to the host due to the capsule. These results suggest that this chemotherapeutic method is effective for human brain tumors.

L20 ANSWER 45 OF 50 MEDLINE on STN
ACCESSION NUMBER: 84180466 MEDLINE

DOCUMENT NUMBER: PubMed ID: 6201270
TITLE: Effects of amphotericin B with combination chemotherapy on response rates and on survival in non-small cell carcinoma of the lung.
AUTHOR: Presant C A; Metter G E; Multhauf P; Bertrand M; Chang F F; Klein L; Rappaport D; Kendregan B; Mackie A
CONTRACT NUMBER: CA-15665 (NCI)
SOURCE: Cancer treatment reports, **(1984 Apr)** 68 (4) 651-4.
Journal code: 7607107. ISSN: 0361-5960.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198405
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 20020125
Entered Medline: 19840530

AB Thirty-seven patients with non-small cell carcinoma of the lung were randomized to receive doxorubicin, lomustine, hexamethylmelamine, and methotrexate (ACHM) or ACHM plus amphotericin B (AMB). The complete plus partial response rate was 39% for ACHM plus AMB, compared to 23% for ACHM alone. However, the median duration of complete or partial response was only 3.0 months with ACHM plus AMB, compared to 7.0 months with ACHM. Most importantly, median survival was only 4.0 months with ACHM plus AMB, compared to 8.0 months with ACHM (P = 0.08; two-tail test). Myelosuppression was enhanced by the addition of AMB. Although AMB has biological and antitumor activity in certain clinical circumstances, it does not appear to have a meaningful role in palliative therapy of patients with non-small cell bronchogenic carcinoma.

L20 ANSWER 46 OF 50 MEDLINE on STN
ACCESSION NUMBER: 80089736 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6243243
TITLE: Phase II study of 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU, NSC Number 409962) with amphotericin B in bronchogenic carcinoma.
AUTHOR: Presant C A; Hillinger S; Klahr C
SOURCE: Cancer, **(1980 Jan 1)** 45 (1) 6-10.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198003
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19900315
Entered Medline: 19800324

AB Eighteen patients with unresectable bronchogenic carcinoma were treated with amphotericin B (7.5 mg/m2 on day 1, 15 mg/m2 on day 2, and 30 mg/m2 on days 3 and 4) plus BCNU (250 mg/m2 on day 4 following amphotericin B) with courses of therapy repeated every 8 weeks. All patients had metastatic disease, and 5 had received prior chemotherapy. Antitumor responses were observed in 8 patients. Six patients had partial responses (greater than 50% decrease in tumor area): 1 of 3 with small cell undifferentiated carcinoma, 1 of 4 patients with large cell undifferentiated carcinoma, 2 of 7 patients with adenocarcinoma, and 2 of

4 patients with epidermoid carcinoma. Two patients had objective improvement (25--50% decrease in tumor area): 1 with small cell undifferentiated carcinoma and 1 with epidermoid carcinoma. The median duration of remission was 3 months. The median duration of survival was 7 months for patients achieving partial response, and only 2 months for other patients. Myelosuppression was the dose limiting toxicity. One patient died with hepatocellular dysfunction, possibly related to BCNU. Transient hypotension was observed in 2 patients. We conclude that amphotericin B plus BCNU produced an encouragingly high response rate in patients with bronchogenic carcinoma, and that a randomized phase III trial is warranted to determine whether amphotericin B enhances the antitumor effects of nitrosoureas or other known antitumor agents.

L20 ANSWER 47 OF 50 MEDLINE on STN
ACCESSION NUMBER: 80020782 MEDLINE
DOCUMENT NUMBER: PubMed ID: 486324
TITLE: The treatment of cutaneous malignancies with topically applied cycloheximide.
AUTHOR: du Vivier A
SOURCE: British journal of dermatology, **(1979 Aug)** 101 (2) 167-9.
Journal code: 0004041. ISSN: 0007-0963.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197912
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19900315
Entered Medline: 19791227

AB Results obtained from an animal test system for epidermal cytotoxic drugs prompted the topical use of 1% cycloheximide in the treatment of histologically confirmed superficial basal cell carcinomata of the skin. Excellent clinical clearing of lesions has been demonstrated and this has been confirmed by post treatment biopsies. Preliminary findings in solar keratoses and intraepidermal carcinomata of the skin are also reported.

L20 ANSWER 48 OF 50 MEDLINE on STN
ACCESSION NUMBER: 79234548 MEDLINE
DOCUMENT NUMBER: PubMed ID: 380801
TITLE: Azaserine, DON, and azotomycin: three diazo analogs of L-glutamine with clinical antitumor activity.
AUTHOR: Catane R; Von Hoff D D; Glaubiger D L; Muggia F M
SOURCE: Cancer treatment reports, **(1979 Jun)** 63 (6) 1033-8. Ref: 35
Journal code: 7607107. ISSN: 0361-5960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197910
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19970203
Entered Medline: 19791017

AB A review of the clinical data on azaserine, DON, and azotomycin reveals that these agents have limited but definite antitumor activity. All three drugs are analogs of L-glutamine and contain a diazo group. They have been studied as single agents in a wide variety of human malignancies and

have also been included in trials using combination chemotherapy. Most of these studies were performed early in the history of clinical trials and, therefore, the method of reporting results and the evaluation criteria were quite different from those in use today. A renewed interest in these agents has been triggered by the remarkable activity of DON and azotomycin against human tumor lines implanted into nude mice. On the basis of this activity and the clinical data we have compiled, we feel that new clinical trials with these agents are warranted.

L20 ANSWER 49 OF 50 MEDLINE on STN
ACCESSION NUMBER: 79134565 MEDLINE
DOCUMENT NUMBER: PubMed ID: 311410
TITLE: Oral anticandidal prophylaxis in patients undergoing chemotherapy for acut- leukemia.
AUTHOR: Williams C; Whitehouse J M; Lister T A; Wrigley P F
SOURCE: Medical and pediatric oncology, **(1977)** 3 (3) 275-80.
Journal code: 7506654. ISSN: 0098-1532.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197905
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19980206
Entered Medline: 19790524

AB Fifty-six untreated patients with acute leukemia (38 acute myelogenous leukemia, 16 acute lymphoblastic leukemia, and 2 blast crisis of chronic granulocytic leukemia) were randomized on admission to one of three groups--one to receive oral anticandidal prophylaxis through the period of remission induction chemotherapy with nystatin, another to receive natamycin, and the third to receive no anticandidal prophylaxis. Neither of the first two groups show any advantage over the last and it is concluded that provided gut sterilization regimes are not employed, prophylactic oral anticandidal treatment is of no value in these patients and should be reserved until there is clinical evidence of infection.

L20 ANSWER 50 OF 50 MEDLINE on STN
ACCESSION NUMBER: 78253573 MEDLINE
DOCUMENT NUMBER: PubMed ID: 356523
TITLE: Prophylactic treatment with miconazole in patients highly predisposed to fungal infection. A placebo-controlled double-blind study.
AUTHOR: Brincker H
SOURCE: Acta medica Scandinavica, **(1978)** 204 (1-2) 123-8.
Journal code: 0370330. ISSN: 0001-6101.
PUB. COUNTRY: Sweden
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 197810
ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19970203
Entered Medline: 19781025

AB In a placebo-controlled double-blind study the prophylactic value of oral systemic treatment with the antimycotic agent miconazole was assessed in 30 highly predisposed patients receiving intensive cytostatic chemotherapy because of haematological malignancies. Patients colonized with Candida before treatment were not freed from this micro-organism by miconazole treatment. However, only 3 out of 6 initially non-colonized miconazole-treated patients became colonized during the study, against 10 out of 10 placebo-treated patients ($p = 0.036$). Seven out of 15 patients in the placebo group developed clinical mycosis, against only two out of 15 in the miconazole group. The miconazole-treated patients remained clinically free of mycosis for 252 out of 264 treatment days, while the placebo-treated patients remained free of mycosis for only 263 out or 338 treatment days ($p = 0.0001$). The results indicate that systemic miconazole treatment protects highly predisposed patients from colonization with Candida and prevents or postpones clinically established candidosis.